Medical University - Varna
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Faculty „Medicine”
Department “ Imaging and interventional radiology”

CT ASSESSMENT OF ABDOMINAL FAT, BONE DENSITY AND SARCOPENIA

ABSTRACT

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"Doctor"

Dr. Dimitrina Nikolova Markova

Area of higher education: 7. Health care and sports,
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Scientific supervisor:
Assoc. Prof. Dr. Chavdar Bachvarov, MD, PhD

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The dissertation contains 203 standard pages and is illustrated with 4 tables and 82 figures. The literary reference includes 511 literary sources, of which 1 in Cyrillic and 510 in Latin.

The dissertation work was discussed and directed for defense to the departmental council of the Department of "Imaging Diagnostics and Interventional Radiology" at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna on …………

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The official defense of the thesis will take place on ……….. of …. o'clock in the Faculty of Medicine - Varna at an open session of the Scientific Jury.

The defense materials are available in the Scientific Department of the Medical University - Varna and are published on the website of the Medical University - Varna.

Note: In the abstract, the numbers of the tables and figures correspond to the numbers in the dissertation work.

CONTENTS

ИЗПОЛЗВАНИ СЪКРАЩЕНИЯ

BMI	Body mass index
CRC	Colorectal carcinoma
CT	Computed tomography
CV	Coefficients of variation
DXA, DEXA	Dual-energy X-ray absorptiometry
FA	Fractional anisotropy
HU	Hounsfield unit
HUAC	Hounsfield Unit Average Calculation
IAAT	Intraabdominal tissue
IFA	Intraperitoneal fat area
IPAT	Intrapelvic tissue
ITAT	Intrathoracic tissue
MRI	Magnetic resonance imaging
PI	Psoas Index
RFA	Retroperitoneal fat area
SAT	Subcutaneous adipose tissue
SFA	Subcutaneous fat area
VAT	Visceral adipose tissue
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio

I. INTRODUCTION

Obesity, and more specifically the accumulation of visceral adipose tissue, is a risk factor associated with many types of diseases [Bergstrom A, et al., 2001, Bianchini F, et al., 2002]. It is also associated with a higher risk of relapse after applied treatment [Ohki T, et al., 2009] and mortality [Calle EE, et al., 2003, Renehan AG, et al., 2008]. Visceral fat is even thought to be an independent risk factor for the development of colon and pancreatic malignancies [Schlienger JL, et al., 2009].

Abdominal adipose tissue can be quantified in several ways: BMI measurement, anthropometry (little used) or through the diagnostic imaging methods CT and MRI. Using BMI is not appropriate because a high figure is not necessarily associated with an increase in visceral fat [Hirooka M, et al., 2005]. In fact, different anthropometric measurements (measurement of thigh circumference, waist or abdominal sagittal diameter) are not reliable [Hirooka M, et al., 2005, Yoshizumi T, et al., 1999] and often confuse visceral fat with subcutaneous fat. In fact, only imaging studies allow examination of both compartments: subcutaneous and visceral fat.

Computed tomography is the most commonly used imaging method because, although it involves the use of ionizing radiation, it is widely available, fast, easy to perform and reliable. Magnetic resonance imaging can also be used [Carlier RY, et al., 2007], the main advantage of which is that it does not use ionizing radiation. However, magnetic resonance imaging has several disadvantages compared to computed tomography: cost (more expensive than computed tomography, more time-consuming, unsuitable for patients with metal implants incompatible with the magnetic field and patients suffering from claustrophobia), accessibility and technical obligations (specific sequences to limit the heterogeneity of the fat segmentation field). The latter disadvantage is serious, since it is not possible to determine the amount of visceral fat retrospectively with MRI. In fact, quantification is only possible with sequences obtained in a specific way.

Computed tomography is a very good technique for segmenting abdominal adipose tissue, as it has several advantages: time saving, reproducibility in standardized activity, accessibility and very low radiation exposure (only one incision is needed), which, given the constant increasing the number of CT scans is an extremely important parameter.

Several studies have been conducted on the methodology for quantifying and measuring abdominal adipose tissue by computed tomography [Hirooka M, et al., 2005; Kobayashi J, et al., 2002; Shen W, et al., 2007; Taira K, et al., 1999; Yoshizumi T, et al., 1999]. In particular, calculation based on the area of a single slice has been shown to be sufficient [Shen W, et al., 2004]. In some studies, weight gain was used as a reference point [Kobayashi J, et al,. 2002, Taira K, et al., 1999; Yoshizumi T, et al., 1999], and in others, bone or disc [Kuk JL, et al., 2006; Lee S, et al., 2004]. To our knowledge, interobserver reproducibility in the calculation of visceral adipose tissue area by computed tomography has never been investigated in the literature. However, it is an essential element of the reliability of a prognostic marker.

II. AIM, TASKS AND HYPOTHESIS

2.1. Aim

To evaluate abdominal adipose tissue, bone density, and sarcopenia parameters using low-dose abdominal CT and analyze their relationship in patients with colorectal carcinoma, lung carcinoma, and patients with chronic pancreatitis.

2.2. Tasks

1) To examine and analyze the distribution and density of subcutaneous and visceral adipose tissue
2) To study and analyze the indicators of sarcopenia - HUAC, Psoas Index (PI)
3) To assess bone density with computed tomography using phantoms
4) To investigate and evaluate the relationship between bone density and subcutaneous and visceral adipose tissue
5) To investigate and assess the relationship between CT indices of subcutaneous and visceral adipose tissue, bone density and sarcopenia
6) To investigate the influence of the inflammatory process on indicators of subcutaneous and visceral fat tissue, bone density and sarcopenia.

2.3. Hypothesis

The excessive accumulation of fat mass could be explained by an increase in the intracellular fat content, without the genesis of new adipocytes and an increase in their number (whose additional organelles would contribute to a higher average density).

III. MATERIAL AND METHODS

3.1. Material

In collaboration with the project "Clinical significance of abdominal visceral adipose tissue in patients with breathing disorders during sleep" led by Prof. Dr. Diana Petkova, MD, 96 patients who have passed through the Clinic were examined by means of low-dose abdominal CT in imaging diagnostics at UMHAT "St. Marina", divided into four groups:

1) patients with colorectal carcinoma – 22 people
2) patients with lung carcinoma - 18 people
3) patients with chronic pancreatitis – 20 people
4) control group – 36 people

The first three groups of patients were retrospectively selected and examined on Siemens Spirit, Somatom Definition and Somatom Force CT scanners, and the subsequent control group was prospectively examined using a Siemens Somatom Force CT scanner. The control group included healthy volunteers.

Criteria for inclusion in the study:

1) Persons over 18 years old.
2) Persons who filled out informed consent for participation in the study
3) Persons with colorectal carcinoma
4) Persons with lung carcinoma
5) Persons with chronic pancreatitis

Exclusion criteria:

1) Persons under 18 years of age.
2) Persons who have not completed informed consent
3) Persons with diseases other than those specified

3.2. Methods

3.2.1. Imaging methods

Patients were scanned with Siemens Spirit, Somatom Definition and Somatom Force computed tomography systems. The studies were carried out natively, and in some of the patients also post-contrast (with intravenous administration of CM) using a low-dose protocol. For the purposes of our study, only the native series in the axial plane were used.

During the scan, a specially developed phantom, created in collaboration with medical physicists, is placed under the lumbar region of the patient. The phantom contains four tubes of liquid of different known contents (distilled water, 0.101 g/mL $CaCl_2$, 0.288 g/mL $CaCl_2$ and 0.365 g/mL $CaCl_2$) – its purpose is to calibrate the images and ensure accurate bone density measurements . [Koch et al. 2021].

Slices are reconstructed in the axial plane, soft tissue window, slice thickness 3 mm. The acquired images are subject to further processing in the open source segmentation program Slicer 3D version 4.11 for volumetric measurements and in RadiAnt for planimetric ones.

Volumetric measurements in Slicer are made by semi-automatic segmentation - a threshold between -190 and -30 Hunsfield Units (HU) is set, which automatically selects all voxels containing adipose tissue. [Solís-Chávez, SA, et al. 2018] Auto-selected voxels outside the region of interest (superior vertebral body lamina L1 to inferior vertebral body lamina L5) were then manually removed from the selection using a slice-by-slice “brush” tool. Any "parasite" voxels automatically marked by the program in intestinal contents and outside the body are also removed. If there is a fat apron, it is preserved in the selected volume, although it is located outside the above limits. If there is a fatty apron, it is preserved in the selected volume. The volume was then further manually segmented into subcutaneous and intra-abdominal compartments. The two separated compartments are quantified by the program – volume data in cubic centimeters and average X-ray density in HU are obtained.

In our study, volumetric determination of the ratio between subcutaneous and intra-abdominal fat tissue was preferred, due to the higher degree of objectivity of the results compared to planimetric (single-slice) measurement.

For the purposes of determining bone density, a L3 vertebral body is manually segmented in Slicer 3D – its volume, mean, median and maximum density in HU in this volume are determined. Additionally, the content of each of the four test tubes is segmented and quantified - average density in HU is reported.

Planimetric measurements were performed entirely manually in RadiAnt – the area and mean density of both psoas muscles were determined at the level of the L4 body pedicles using native CT images. Area is calculated by outlining muscle contours, average density by circular or elliptical region of interest. Using these values, HUAC (Hounsfield Unit Average Calculation) and Psoas Index (PI) were calculated as markers of sarcopenia. [Boutin RD, et al. 2015; Yoo T, et al. 2017]. Lower HUAC values define lower muscle mass.

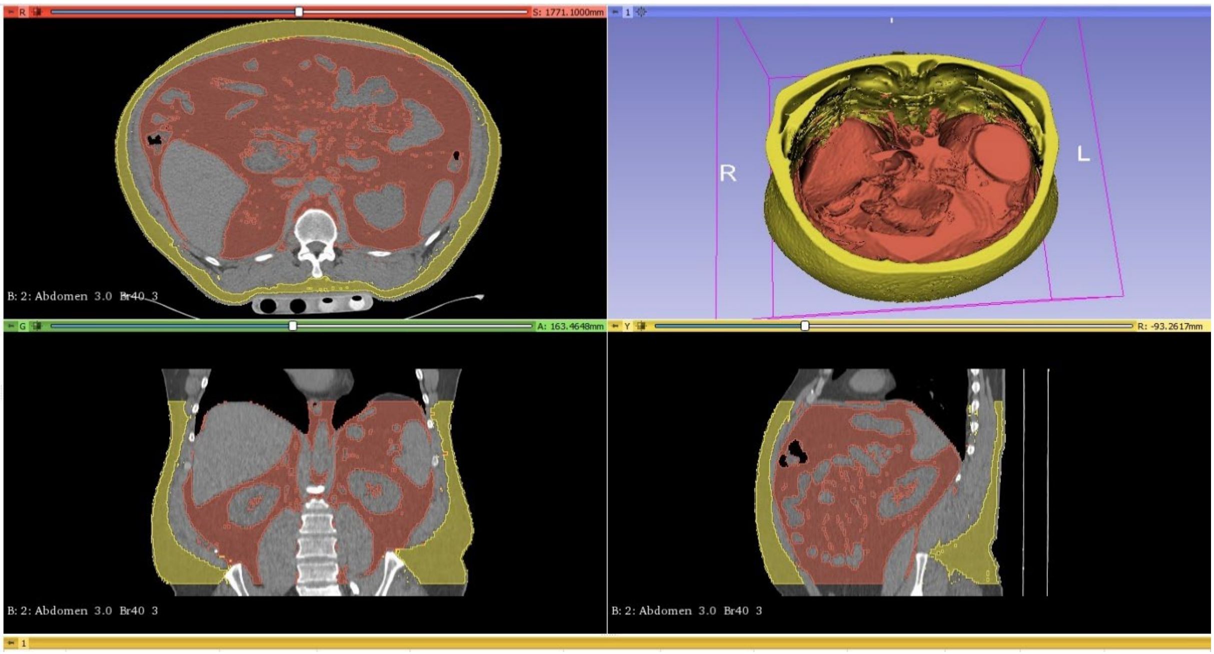

Fig. 1. Generated 3D Slicer User Interface - MRP+VRT - author's image of Assoc. Prof. Valchev

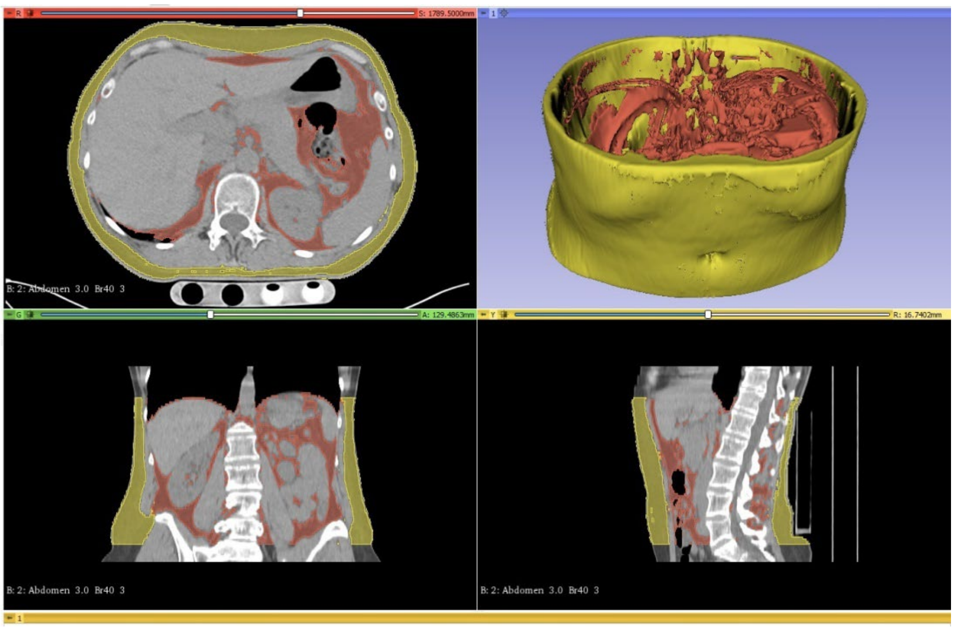

Fig. 2. A sample of the Slicer 3D work interface when the segmentation is complete - two-dimensional slices in the three principal planes are shown on a black background, and the final three-dimensional model is demonstrated in the upper right. The subcutaneous adipose tissue is indicated in yellow, and the visceral adipose tissue in red. The segmentation was carried out in collaboration with the project "Clinical significance of abdominal visceral adipose tissue in patients with breathing disorders during sleep". - Author image of Assoc. Prof. Dr. Georgi Valchev

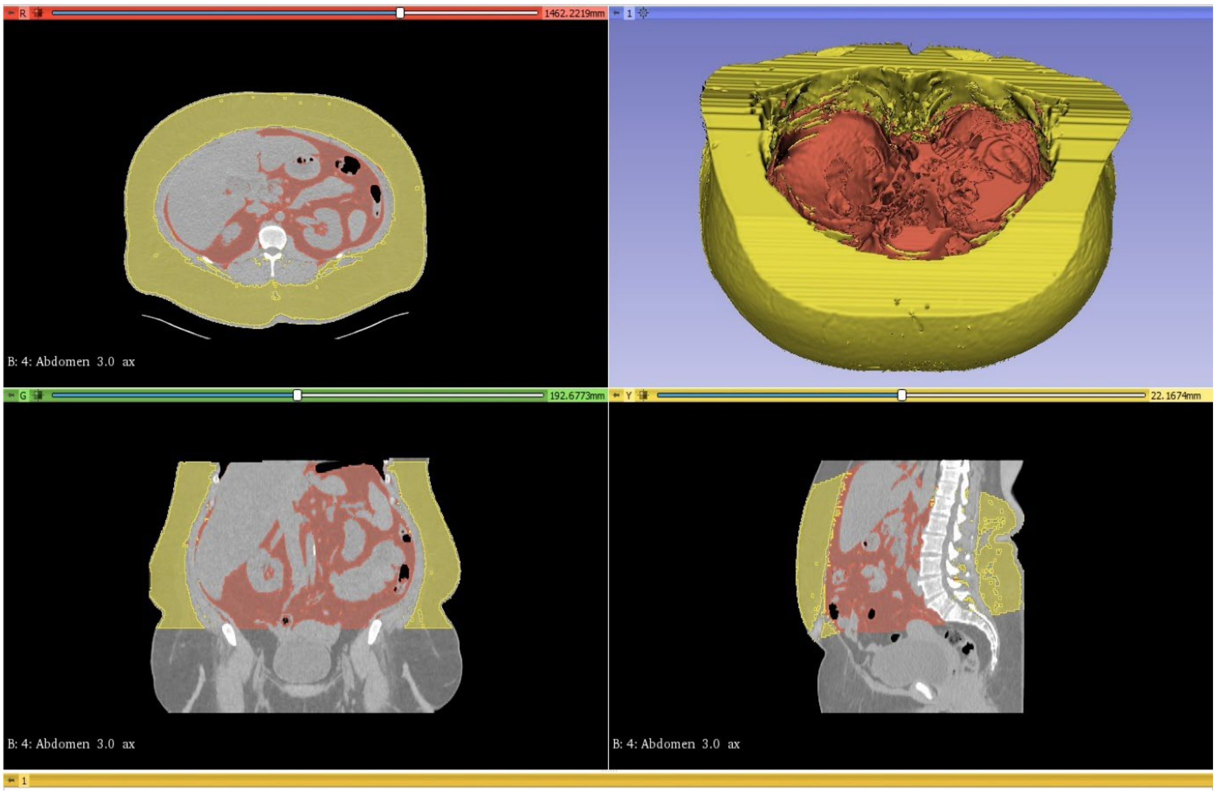

Fig. 3. 3D Slicer User Interface - MRP+VRT - author's image of Assoc. Prof. Valchev

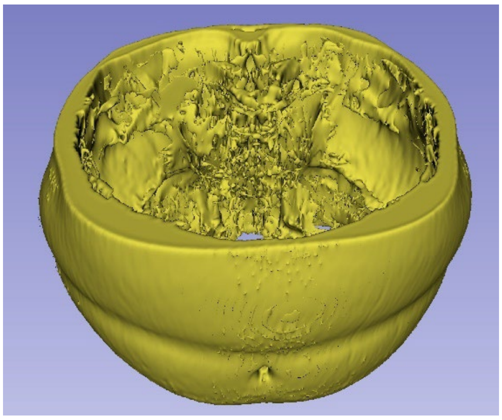

Fig.4. Slicer 3D generated 3D model of subcutaneous fat tissue after segmentation completed - top and front view. Author's image of Assoc. Prof. Georgi Valchev

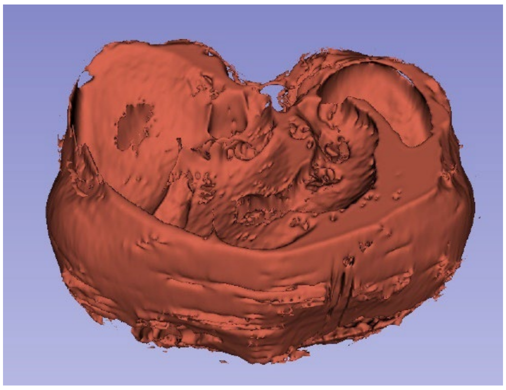

Fig. 5. Slicer 3D generated 3D model of visceral fat tissue after segmentation completed - front view.

Author's image of Assoc. Prof. Georgi Valchev

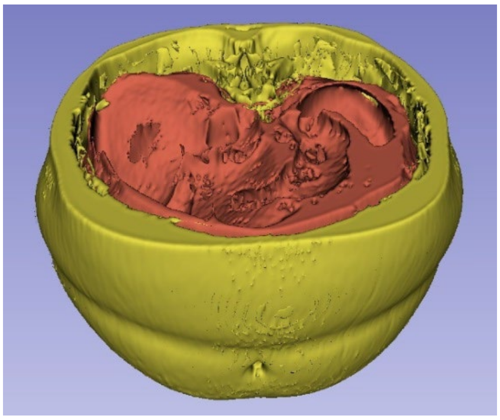

Fig. 6. Slicer 3D generated 3D model of subcutaneous and visceral fat together after segmentation completed - front and top view. Author's image of Assoc. Prof. Georgi Valchev

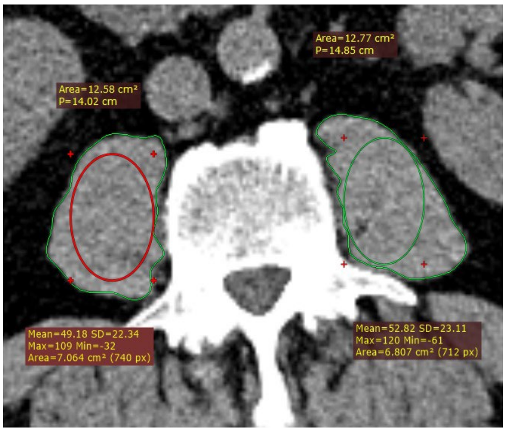

Fig.7 Low-dose CT abdomen. Measurement of HUAC and psoas index by determining the area and mean density of the psoas muscles at the L4 level. Manually outline the circumference of both psoas with an irregular closed polygon highlighted in green. The ellipse measures the average density of the two psoas, with the measurement of the right one marked in red. The designations in the top row correspond to the cross-sectional area of the psoas muscles. The labels in the bottom row correspond to the measured average density in the ellipses. Author's image of Assoc. Prof. Georgi Valchev

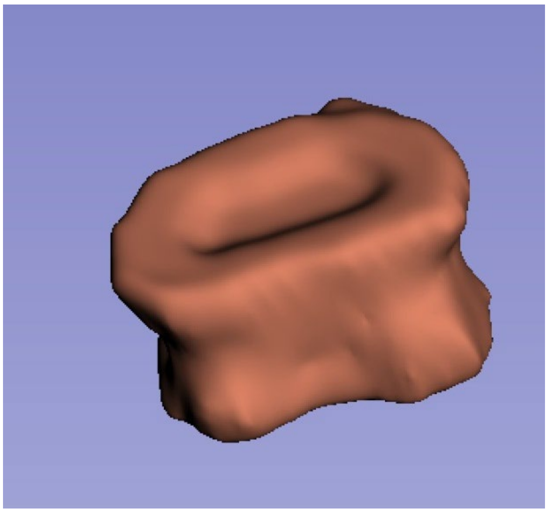

Fig. 8. Three-dimensional volumetric model of the body of L3 obtained on Slicer.

Author's image of Assoc. Prof. Georgi Valchev

3.5.2. Anthropometric indicators

- BMI – body mass index is an indicator that serves to determine a normal, healthy weight and serves to diagnose obesity and malnutrition. The body mass index is measured in kilograms per square meter and is determined by the following formula:

$$BMI = \frac{W}{h^2},$$

Where: W – weight in kilograms
h – height in meters

mild malnutrition: 17 – 18,49
overweight: ≥ 25,0
normal weight: 18,5 – 24,99
moderate malnutrition: 16 – 16,99
severe malnutrition: < 16,0
obesity: ≥ 30,0

- In the present study, it will be used to evaluate the accuracy of imaging methods in measuring adipose tissue by comparing the indicators.

3.5.3. Laboratory indicators

- ESR - erythrocyte sedimentation rate - to assess the presence of an inflammatory process in the body. Since the indicator is not specific, it is combined with CRP. The present study will evaluate the relationship between adipose tissue, ESR, and CRP using abdominal CT and the risk of onset and development of inflammation. Reference value: men - 1-15 mm/h; women - 1-20 mm/h
- CRP - C-reactive protein - is used as a marker for inflammation in the body. Reference value <0.5 mg/dL.
- Leukocytes - Leukocytes are white blood cells. They are one of the formed elements of the blood, through the examination of which various diseases can be established. One of the reasons for an

increase in the number of leukocytes is most often a bacterial infection. And a decreased number can be a sign of viral diseases such as the flu or chicken pox. An increase in the number of these cells is called leukocytosis, and a decrease is called leukopenia. Reference values: 3.5 - 10.5 giga per liter.

- Glucose – this indicator will be used to assess the risk of the development of diabetes mellitus with increased levels of adipose tissue detected with the help of CT and the possibility of imaging methods to participate in the diagnosis of metabolic diseases will be evaluated.

3.5.4. Statistical methods

The statistical software package - IBM SPSS for Windows, v.20.0 was used for data processing.

In all the analyzes conducted, an acceptable significance level of $p<0.05$ with a confidence interval of 95% is accepted.

- Analysis of Variance (ANOVA) to assess how much the influence of a given factor is statistically significant or not.
- Variance analysis to study the quantitative characteristics of indicators.
- Analysis to assess the risk of an event occurring (OR, HR, RR).

  Correlation analysis to assess the dependence between the studied indicators. The assessment of the strength of the relationship between the variables is based on the results of Pearson's coefficient (r) and Spearman's coefficient (p), with Spearman's coefficient calculating the correlation based on monotonic relationships and Pearson's coefficient based on linear relationships. The degree of association between variables is defined as:
  - 0<r(p) <0.3 – poor correlation
  - 0.3<r(p) <0.5 – moderate correlation
  - 0.5<r(p) <0.7 – significant correlation
  - 0.7<r(p) <0.9 – strong correlation
  - 0.9<r(p) <1 – very strong correlation
- Regression analysis to assess the possible functional dependencies between the investigated indicators. Causal research..
- Comparative analysis (hypothesis evaluation) – $\chi 2$, Student's t-test for comparing quantitative and qualitative indicators and studying the difference between them.
- Graphical and tabular method of displaying the obtained results.

The study was conducted after receiving permission from the Committee on Ethics of Scientific Research at MU-Varna - Minutes/Decision No. 103, meeting on 05/27/2021.
All study participants signed an informed consent.

IV. RESULTS

4.1. Examination and analysis of the distribution and density of subcutaneous and visceral adipose tissue

96 patients who went through the Imaging Clinic at the UMHAT "St. Marina" with an average age of 61.09 years (Fig. 9). The distribution of the total sample by gender shows that men predominate (73.96%).

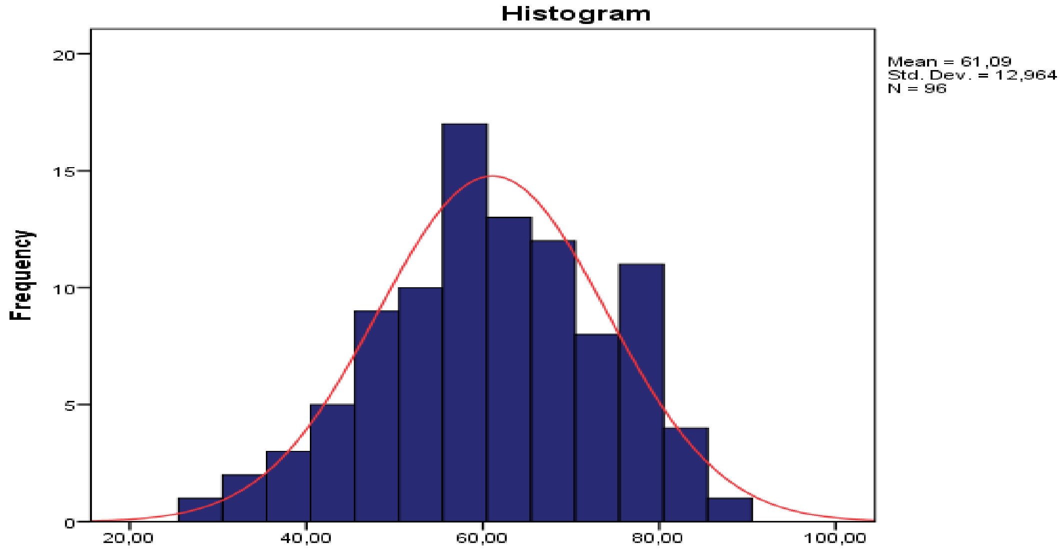

Fig. 9. Distribution by age of patients

The distribution of the examined persons by group is presented in fig. 10 and shows that patients from the control group have a slight advantage over the others.

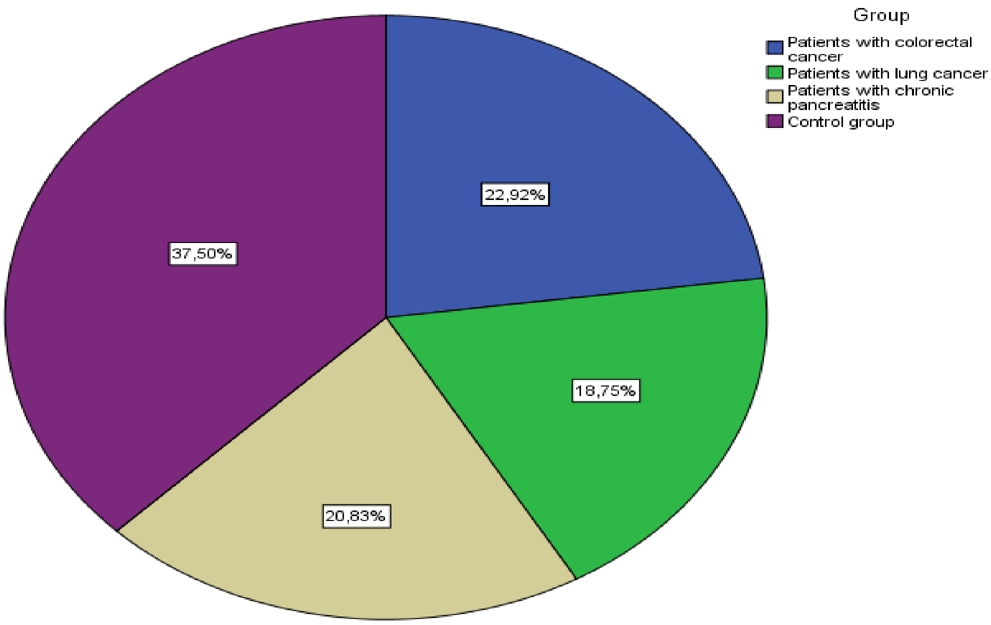

Fig. 10. Distribution of patients according to the studied groups

A significant difference in age was found between the examined groups of patients ($p<0.001$) (Fig. 11).

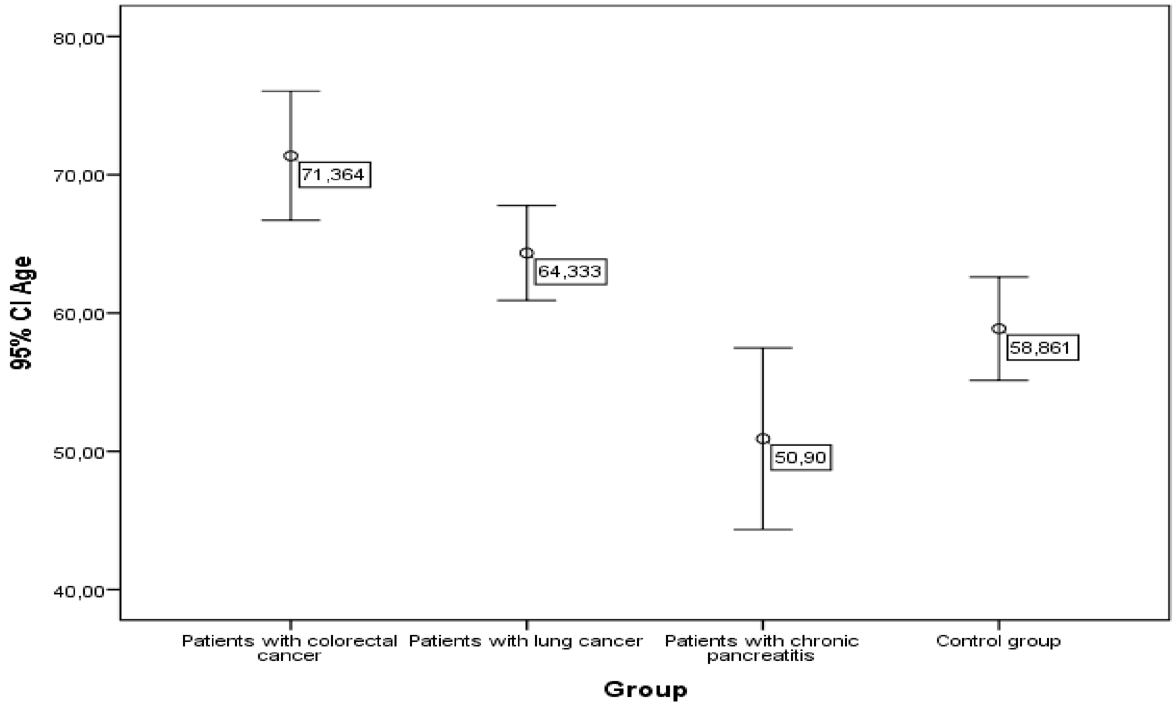

Fig. 11. Average age of patients in the studied groups

The results in fig. 12 show the gender distribution of the studied patients between the groups.

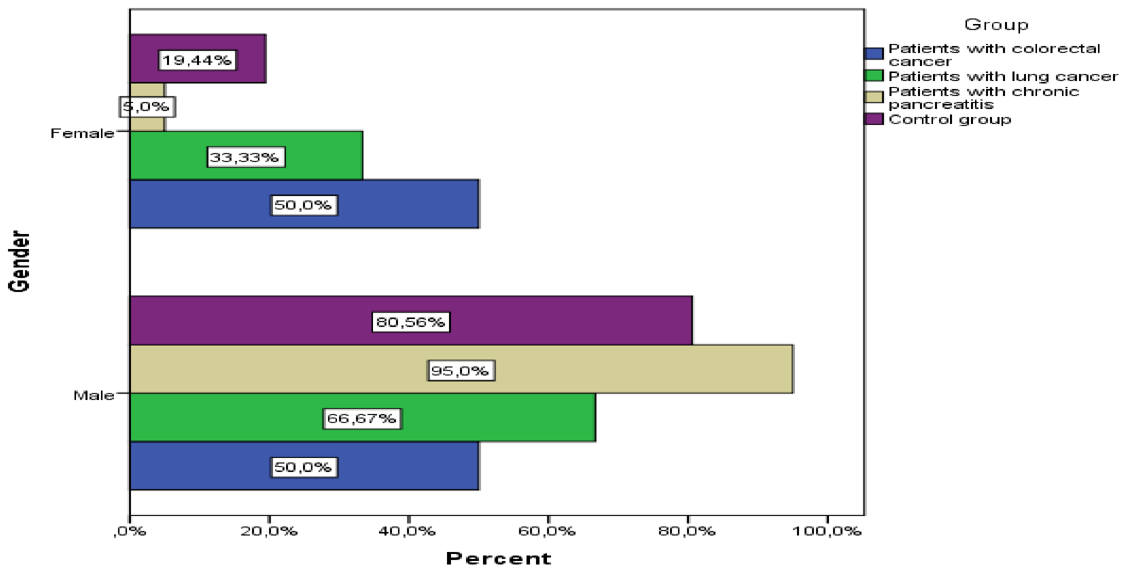

Fig. 12. Gender distribution of patients in the studied groups

The mean volume of SAT was 6700.58±5030.21 cm3 (514 – 24021.10 cm3), and a significant difference was found between the groups of patients under consideration ($p<0.001$) (Fig. 13). Patients from the control group had the largest volume of subcutaneous adipose tissue (mean 10234.53 cm3),

while patients with chronic pancreatitis and patients with lung carcinoma had the smallest volume of SAT (3377.10 cm3 and 3474.86 cm3, respectively) (Fig. 14).
A moderate correlation was found between the studied groups of patients and the SAT volume ($r=0.335$; $p=0.001$), which shows that the disease correlates with the SAT volume.

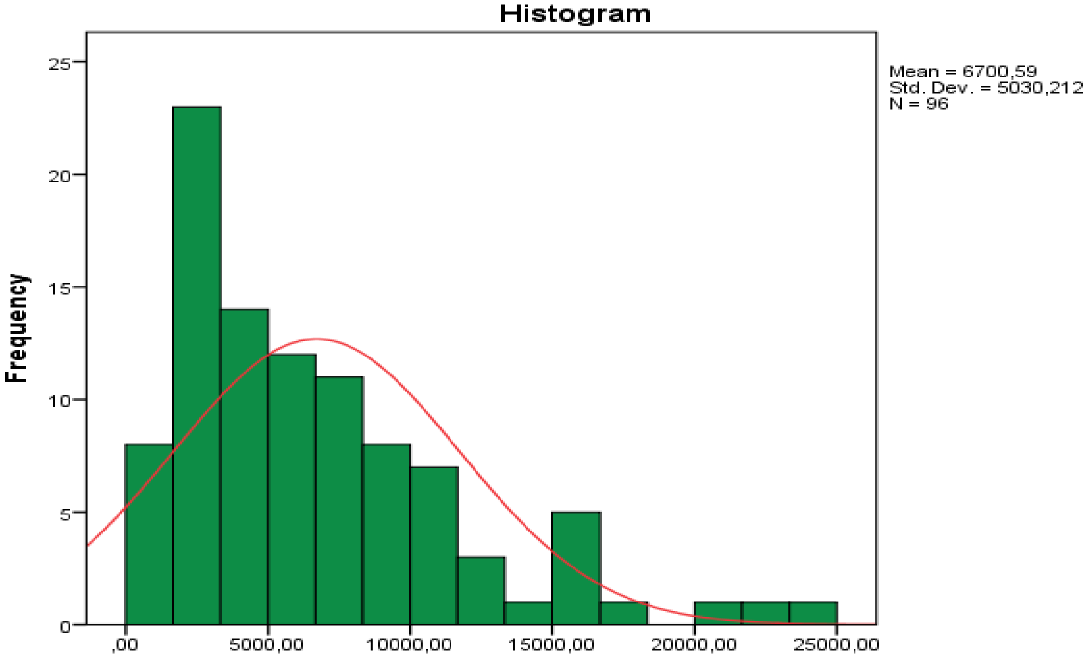

Fig. 13. Distribution of patients according to the volume of SAT

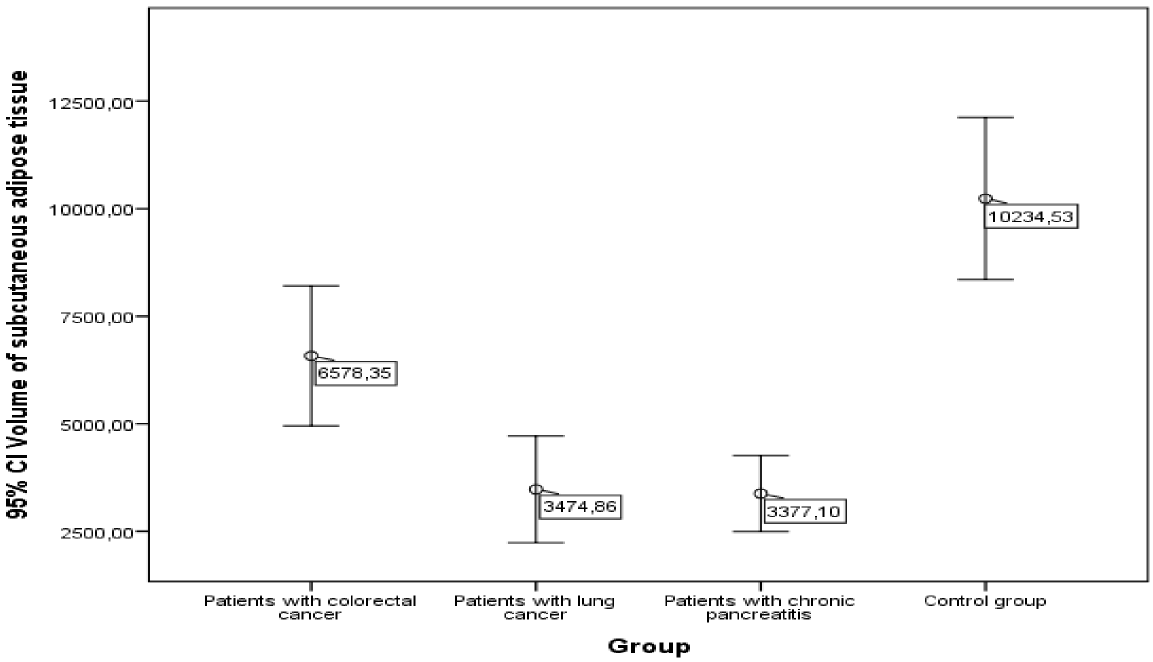

Fig. 14. Average volume of subcutaneous adipose tissue according to the considered groups of patients

Colorectal carcinoma was associated with greater SAT volume, whereas lung carcinoma and chronic pancreatitis correlated with lower SAT volume.

No correlation was found between age and the volume of subcutaneous fat tissue, but a weak to moderate correlation was found with the gender of the examined patients (r=0.289; p=0.004) - in all studied groups, a greater volume of SAT was found in women in compared to men (Fig. 15).

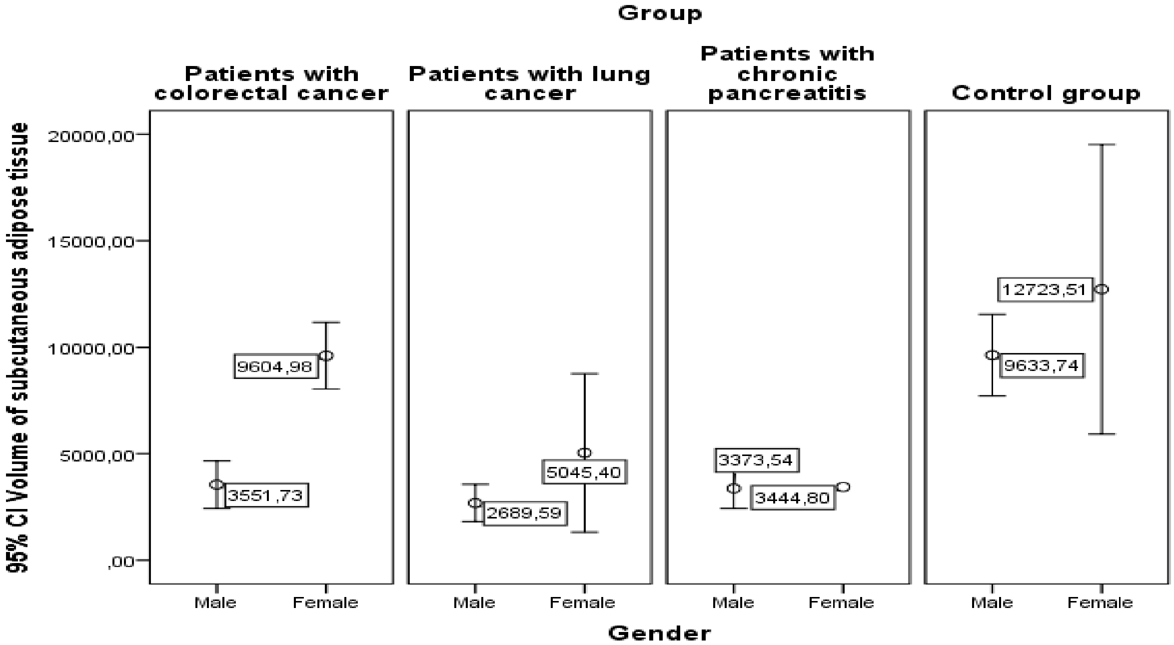

Fig. 15. Average volume of subcutaneous adipose tissue according to gender and the studied group of patients

The average volume of VAT was 4944.94±3220.7898 cm3 (512.60 – 14806.50 cm3), and a significant difference was found between the considered groups of patients (p<0.001) (Fig. 16). Patients in the control group had the highest VAT volume (mean 7746.98 cm3), while lung cancer patients had the lowest VAT volume (2875.28 cm3).

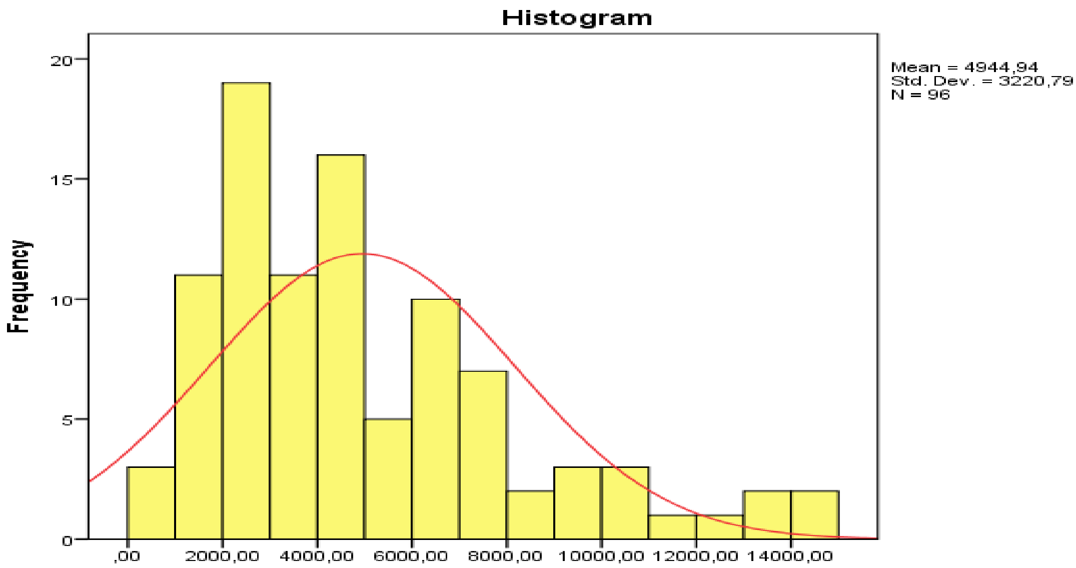

Fig. 16. Distribution of patients according to the volume of visceral adipose tissue

A significant correlation was found between the studied groups of patients and the VAT volume (r=0.518; p=0.001), which shows that the presence of any of the studied diseases correlates with the VAT volume. Lung carcinoma was associated with a smaller VAT volume, whereas colorectal carcinoma with a larger VAT volume (Fig. 17).

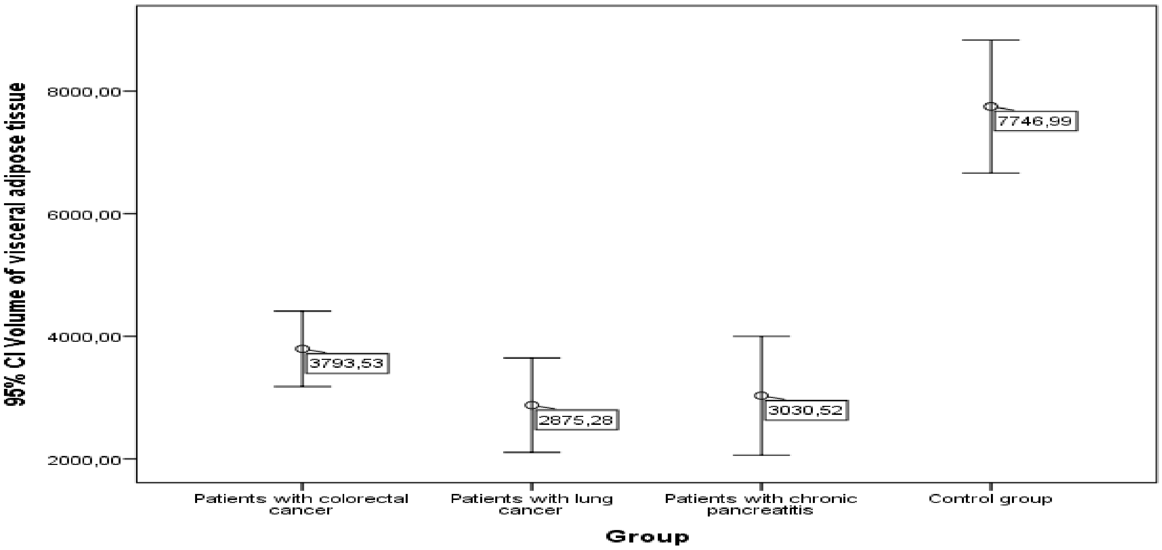

Fig. 17. Average volume of visceral adipose tissue according to the considered groups of patients

No relationship was found between age and gender and VAT volume. In patients with lung carcinoma, chronic pancreatitis, and the control group, a greater VAT volume was found in men, while in patients with colorectal cancer, a greater VAT volume was observed in women (Fig. 18).

In all four studied groups, a greater mean volume of SAT was observed compared to VAT. The difference was most pronounced in the patients from the control group (respectively, on average 10,235 cm3 for SAT volume and on average 7,747 cm3 for VAT volume) and in the group of patients with colorectal carcinoma (respectively, 6,578.4 cm3 for SAT volume and 3,793.5 cm3 for the volume of VAT) (Fig. 19.).

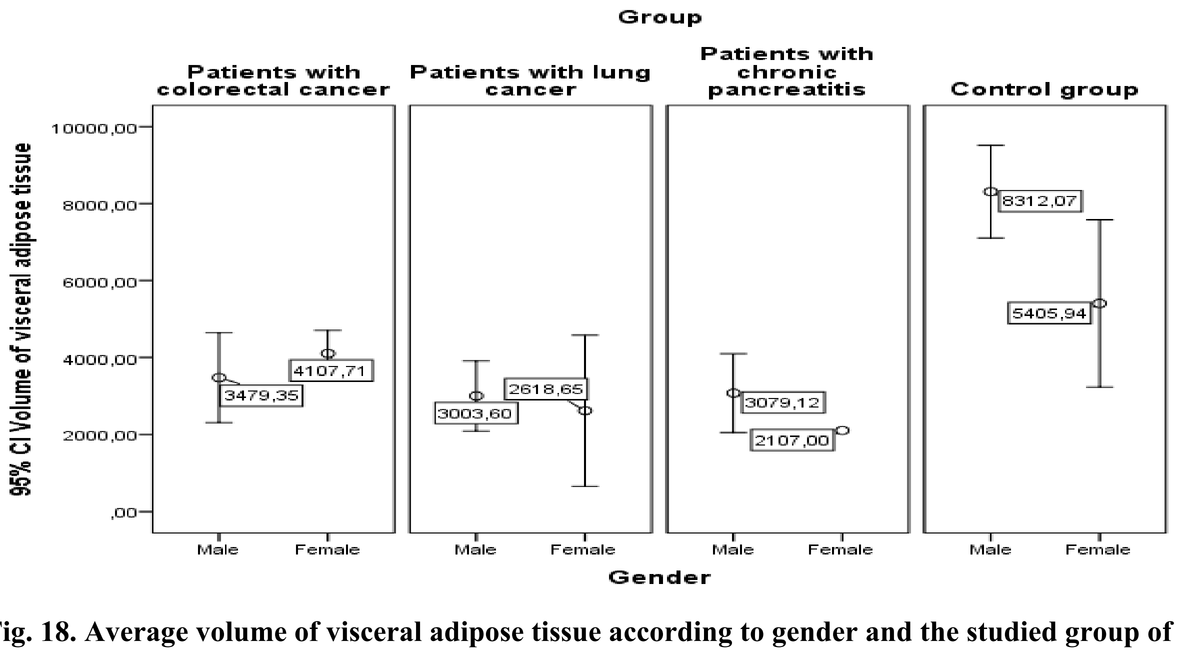

Fig. 18. Average volume of visceral adipose tissue according to gender and the studied group of patients

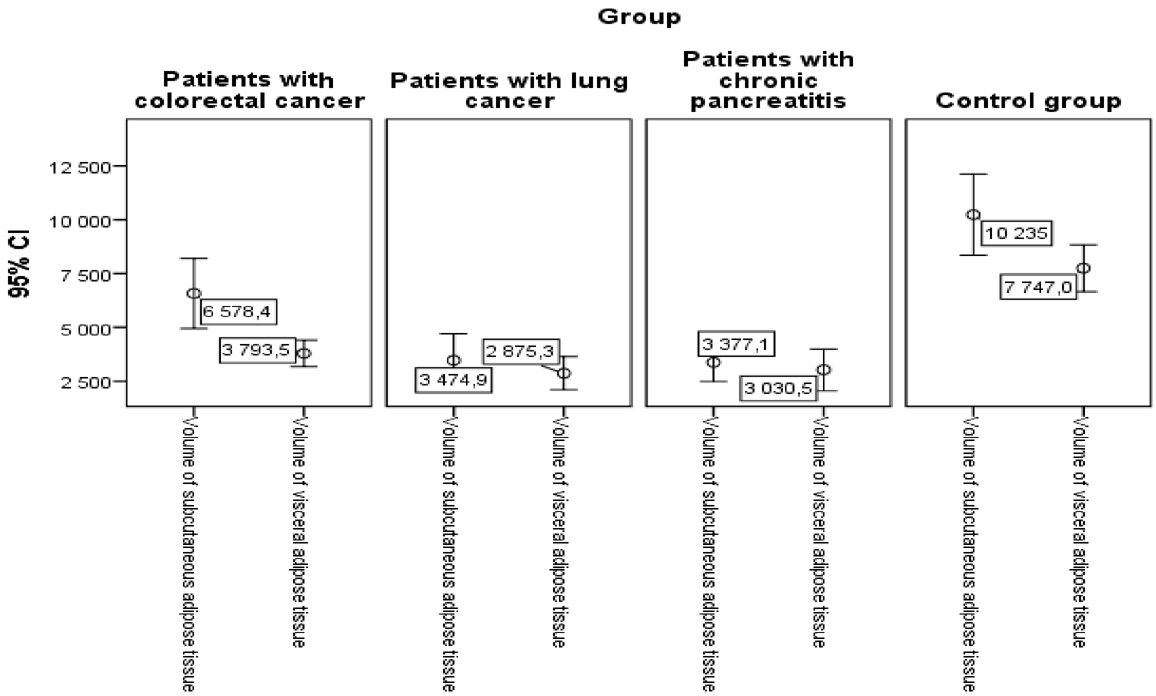

Fig. 19. Average volume of subcutaneous and visceral adipose tissue in the studied groups of patients

The mean density of VAT was -85.38±10.14 HU (-103.75 - 62.62 HU), establishing a significant difference between the considered groups of patients ($p<0.001$) (Fig. 20). Patients in the control group had the lowest VAT density (-93.67 HU), while patients with chronic pancreatitis had the greatest VAT density (-77.91 HU) (Fig. 21).

A moderate correlation was found between the studied groups of patients and SAT density ($r=-0.319$; $p=0.002$), which indicates that the disease correlates with SAT density.

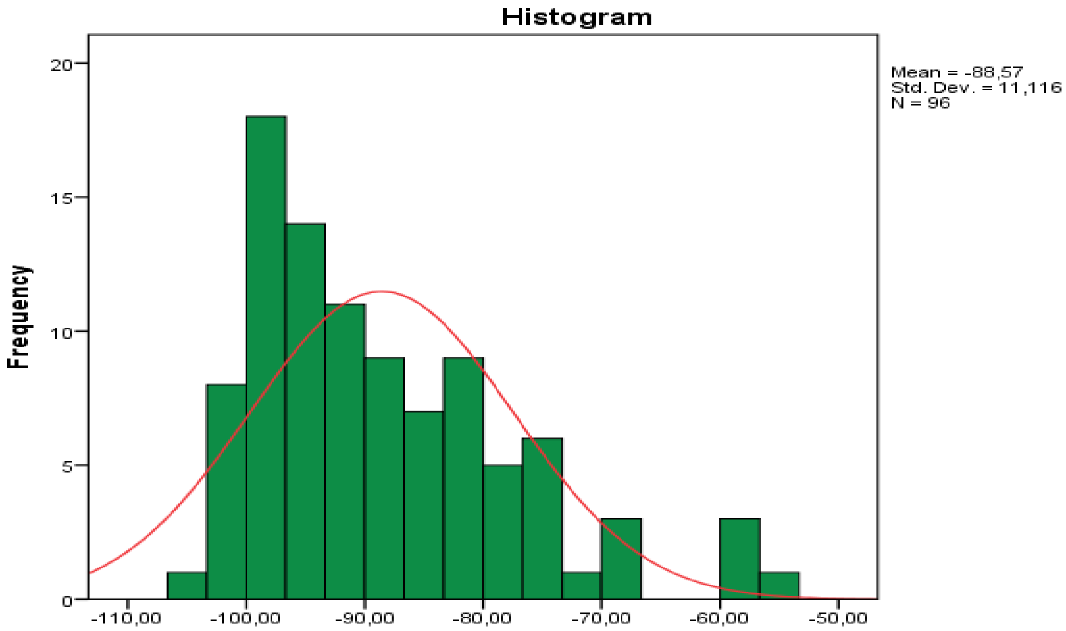

Fig. 20. Distribution of patients according to the density of subcutaneous fat tissue

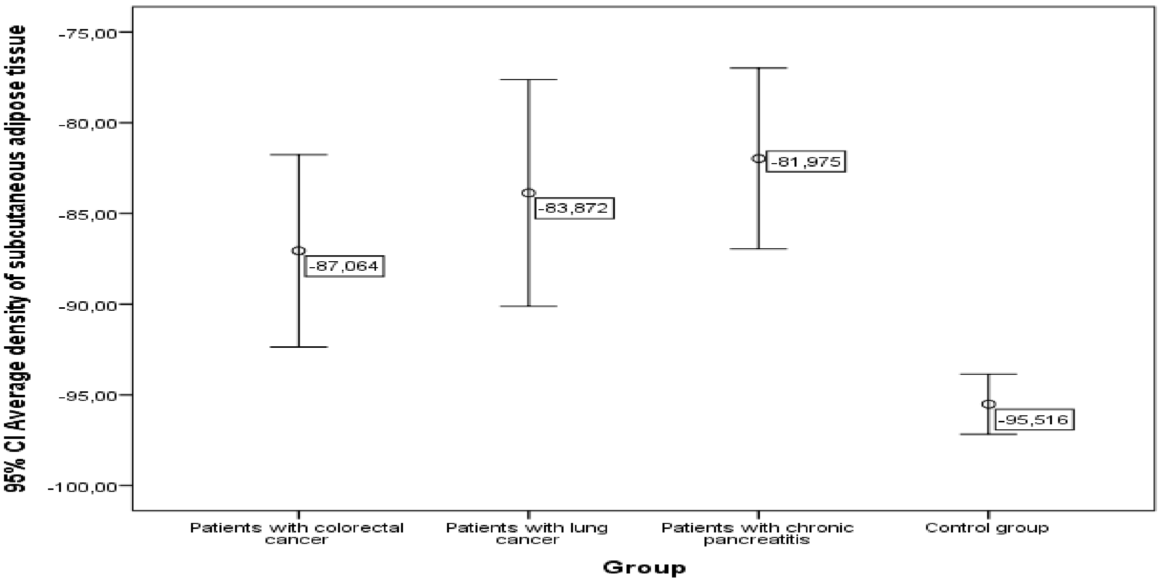

Fig. 21. Average density of subcutaneous adipose tissue according to the patient groups under consideration

No correlation was found between age and the density of subcutaneous fat tissue, but a weak to moderate correlation was found with the gender of the studied patients (r=-0.284; p=0.004). In all studied groups, a greater density of SAT was found in women compared to men (Fig. 22).

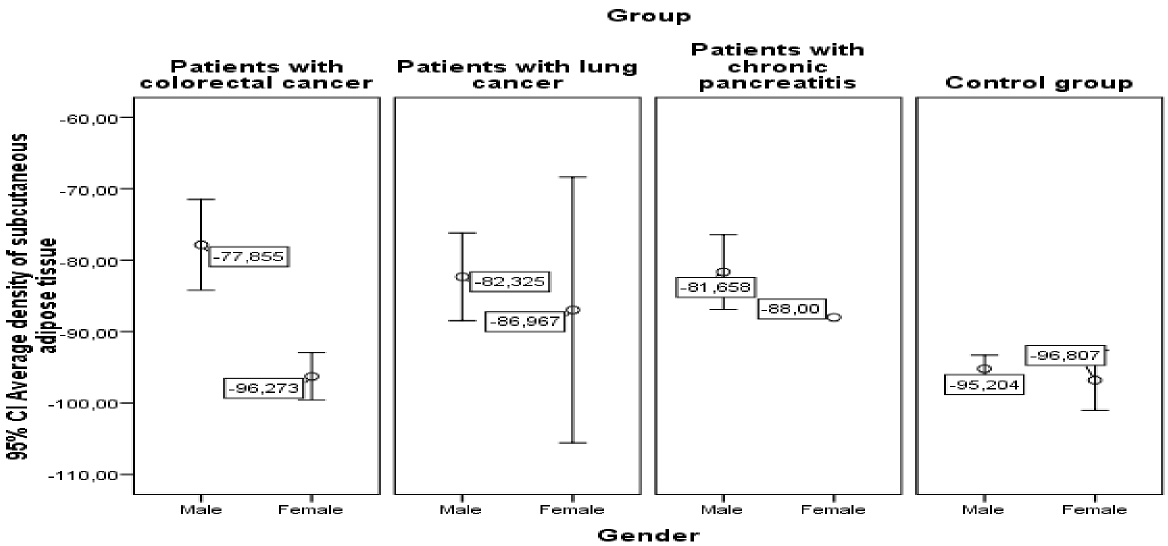

Fig. 22. Average density of subcutaneous adipose tissue according to gender and the studied group of patients

The mean VAT density was -85.38±10.14 HU (-103.75 - 62.62 HU) (Fig. 23), and a significant difference was found between the considered groups of patients (p<0.001). Patients in the control group had the lowest VAT density (-93.67 HU), while patients with chronic pancreatitis had the greatest VAT density (-77.91 HU) (Fig. 24).

A moderate correlation was found between the studied groups of patients and the density of visceral adipose tissue (r=-0.448; p=0.001), which indicates that the disease correlates with the density of visceral adipose tissue.

No relationship was found between age and gender and the density of subcutaneous fat. In patients with colorectal and lung carcinoma, a greater density was observed in women, while in the other groups, the density of VAT was greater in men (Fig. 25).

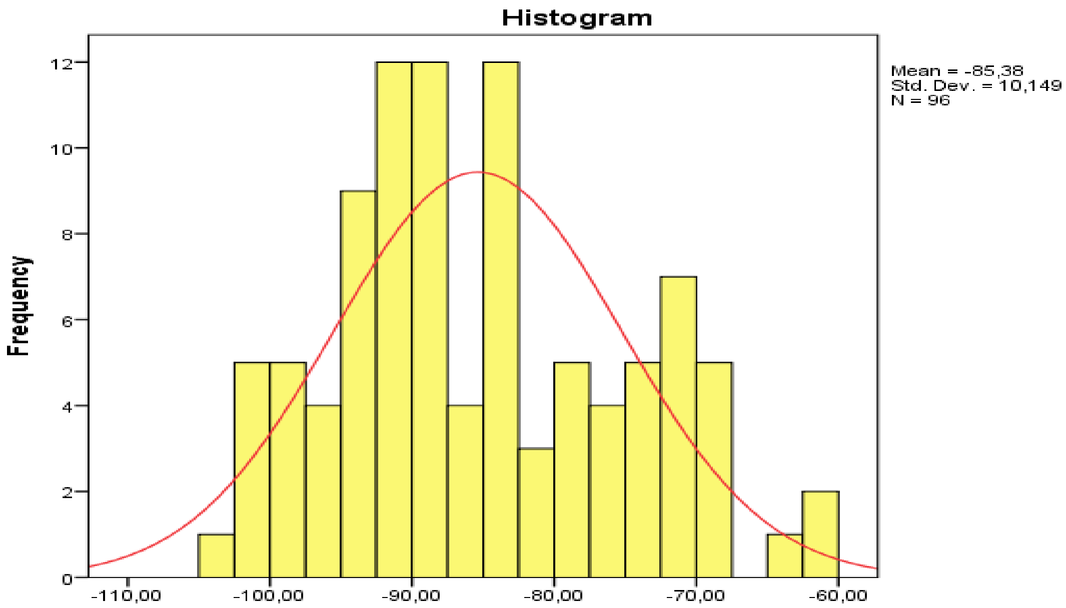

Fig. 23. Distribution of patients according to the density of visceral adipose tissue

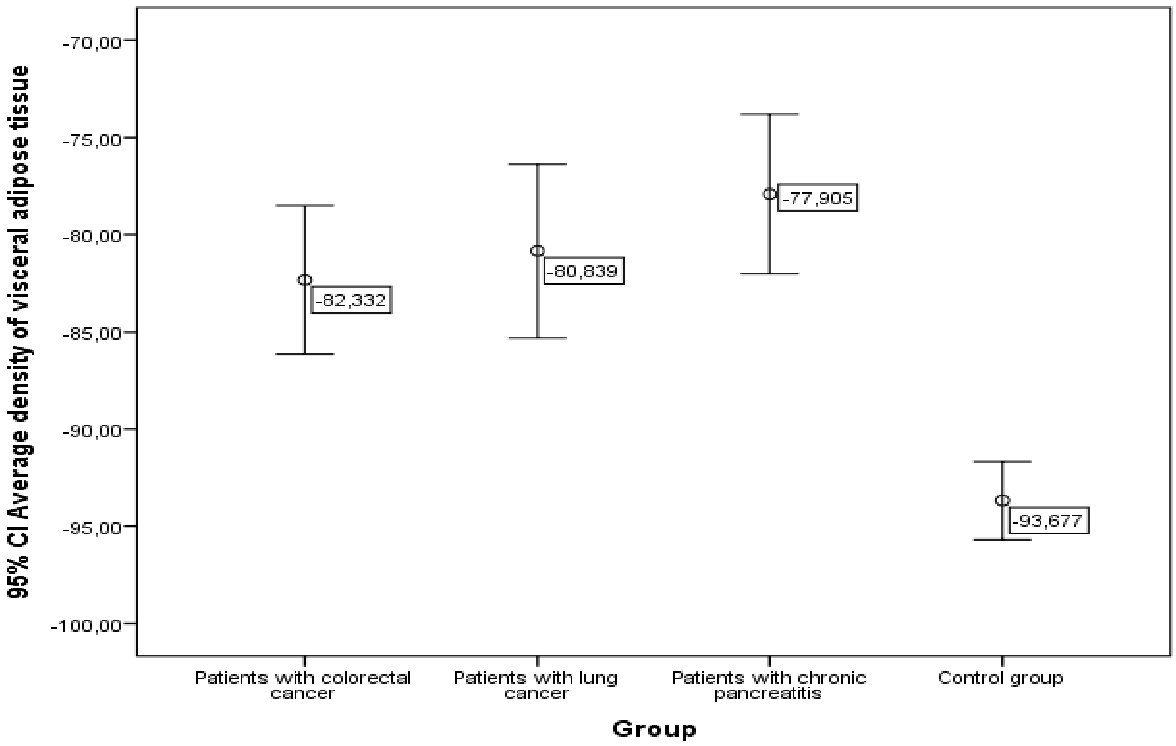

Fig. 24. Average density of visceral adipose tissue according to the considered groups of patients

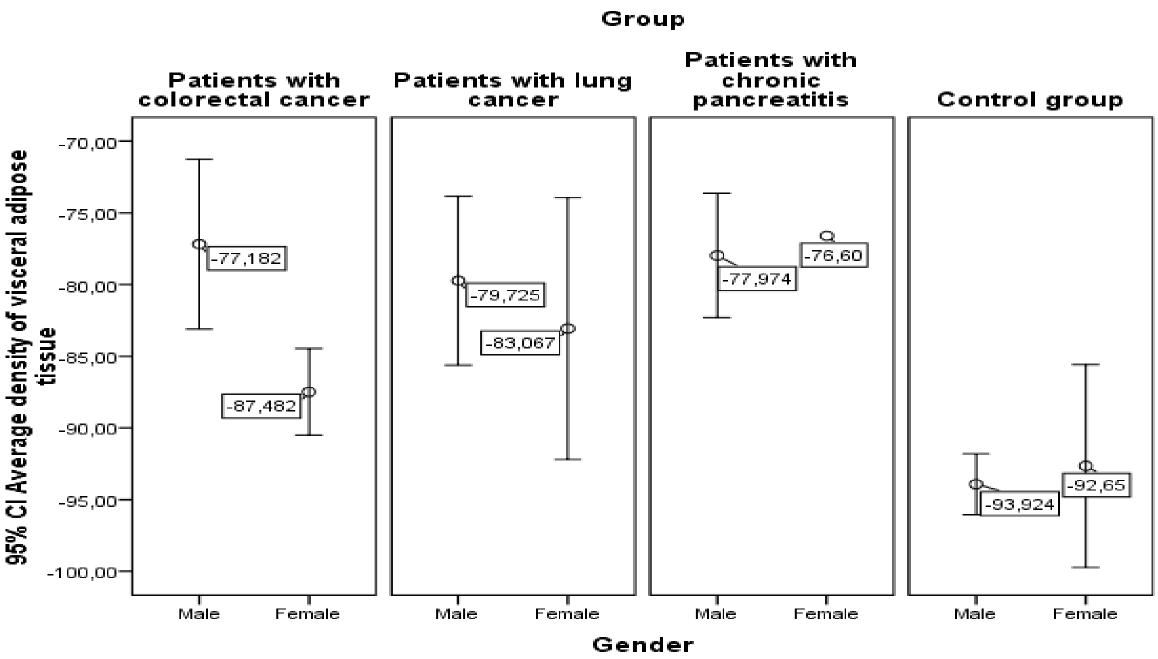

Fig. 25. Average density of visceral adipose tissue according to gender and the studied group of patients

A lower density of subcutaneous adipose tissue (SAT) compared to visceral adipose tissue (VAT) was observed in all four studied groups. (Fig. 26.).

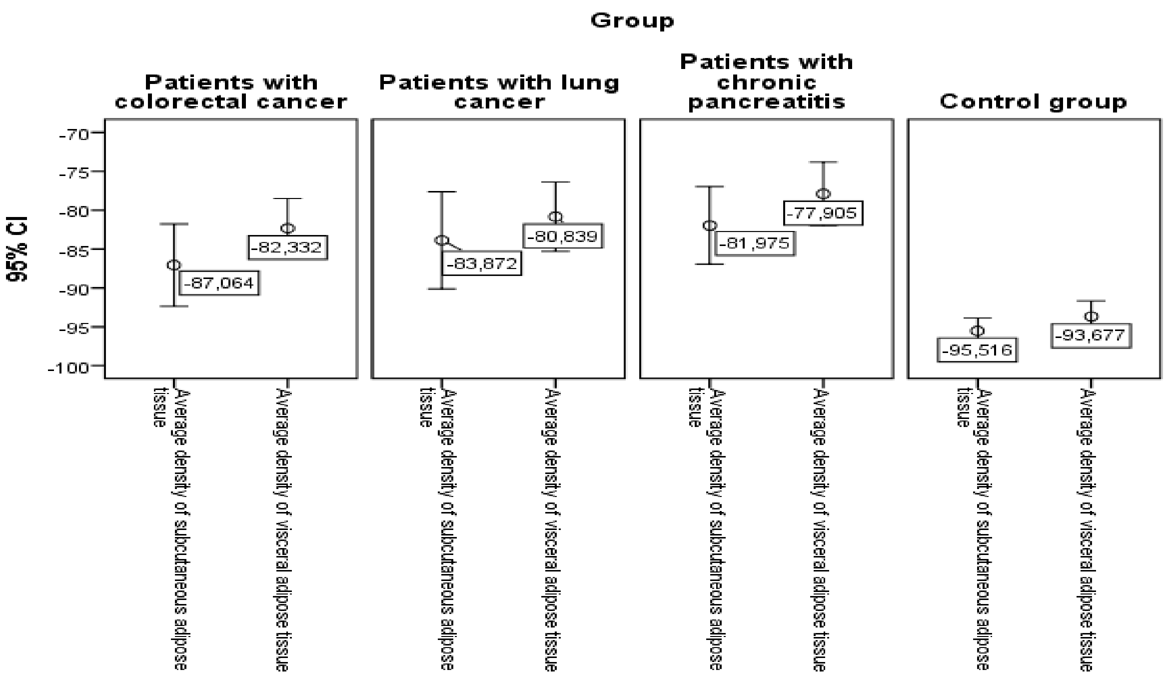

Fig. 26. Average density of subcutaneous and visceral adipose tissue in the studied groups of patients

A moderate inverse correlation was found between the volume and density of SAT (r=-0.468; p<0.001), which indicates that an increase in SAT volume leads to a decrease in density - this could be explained by an increase in intracellular fat content, without the genesis of new adipocytes (whose additional organelles would contribute to a higher average density) (Fig. 27.).

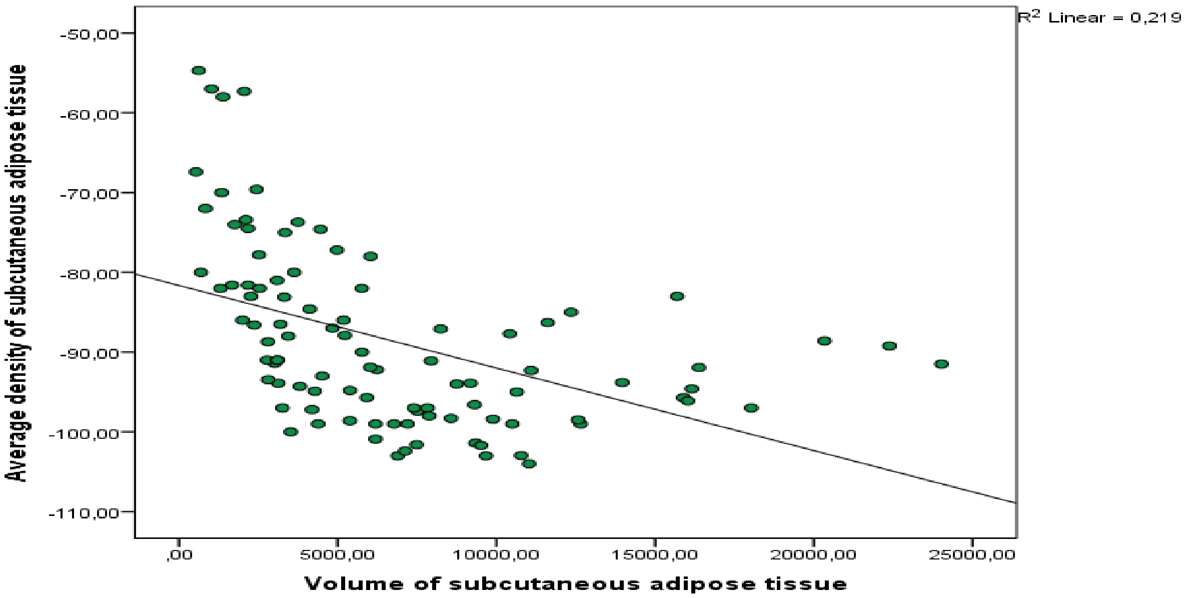

Fig. 27. Dependence between the volume and density of subcutaneous fat tissue

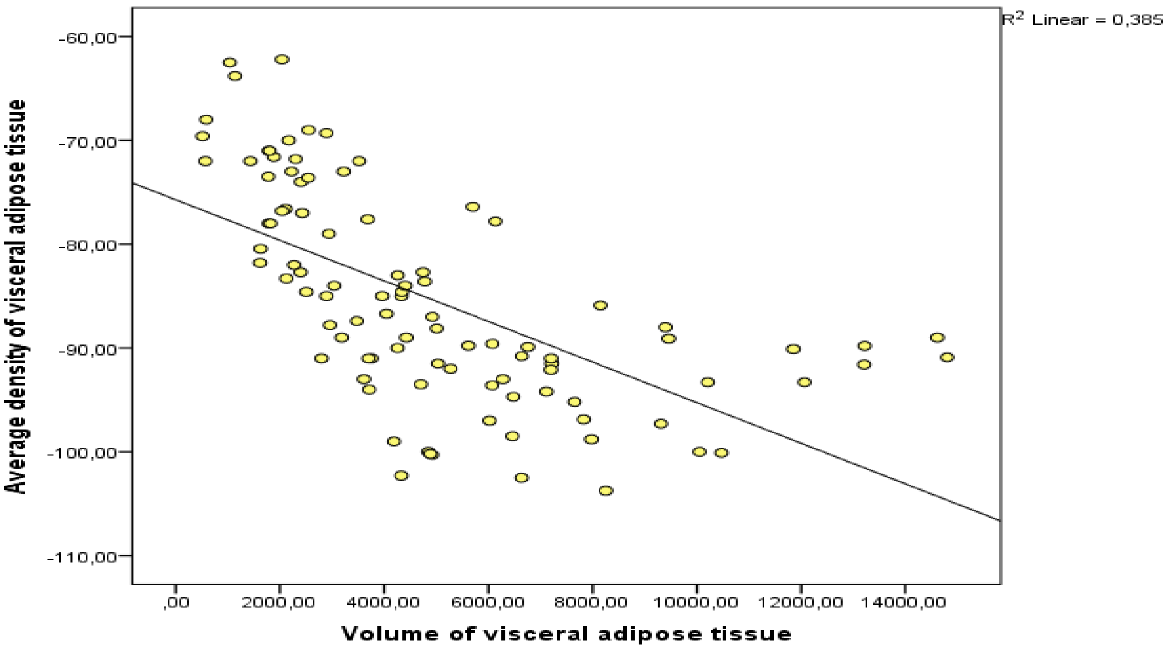

Fig. 28. Dependence between volume and density of visceral adipose tissue

A significant inverse correlation was found between volume and BMT density ($r=-0.620$; $p<0.001$), indicating that an increase in BMT volume leads to a decrease in density. The potential explanation is analogous to that indicated above (Fig. 28.).

4.2. To examine and analyze Sarcopenia indicators - HUAC, Psoas Index (PI)

Two indicators of sarcopenia HUAC and Psoas Index (PI) were studied and analyzed. HUAC was calculated in all studied patients, while Psoas Index was calculated in 33 patients.

A significant difference was found in the mean values of HUAC in patients from the four studied groups (p=0.003), with the lowest values in patients with colorectal carcinoma (40.5) and the highest value in individuals from the control group (Fig. 29). A moderate correlation was found between HUAC values and the presence of a given disease in the studied groups of patients (r=0.362; p<0.001). Higher HUAC values in the study cohort were associated with the presence of lung carcinoma or chronic pancreatitis.

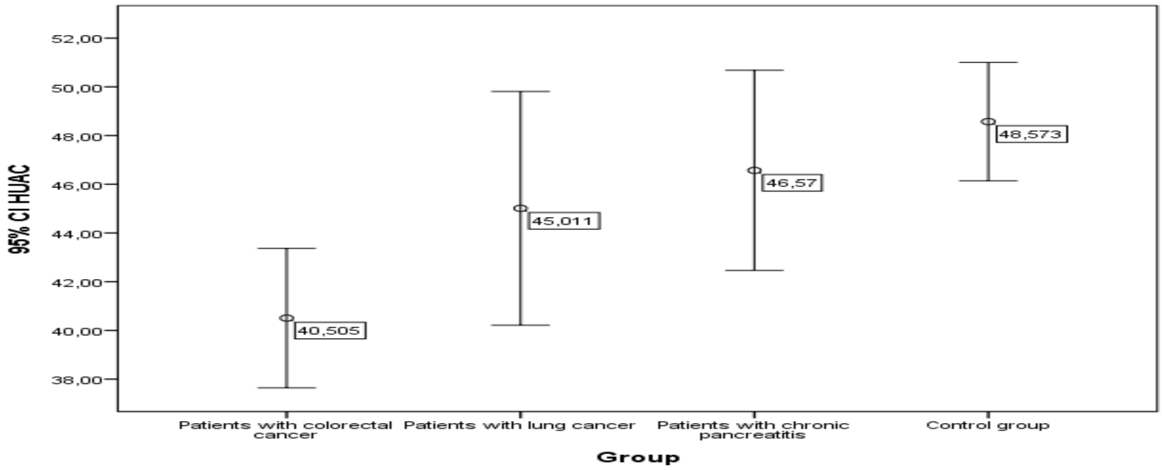

Fig. 29. Mean values of HUAC according to the study group

Although no relationship between gender and HUAC was found in the literature, a moderate relationship between gender and HUAC was found in the present study in colorectal cancer patients (r=0.371; p<0.001), with women having lower HUAC values than men. Lower HUAC values in women were also observed in patients with chronic pancreatitis, while no significant gender difference was found in the control group (Fig. 30.).

The study of the relationship of HUAC with age established an inversely proportional moderate dependence (r=-0.324; p=0.001), which shows that increasing age leads to a decrease in the value of HUAC (Fig. 31) - a logical result in view of physiological hypotrophy. occurring with aging.

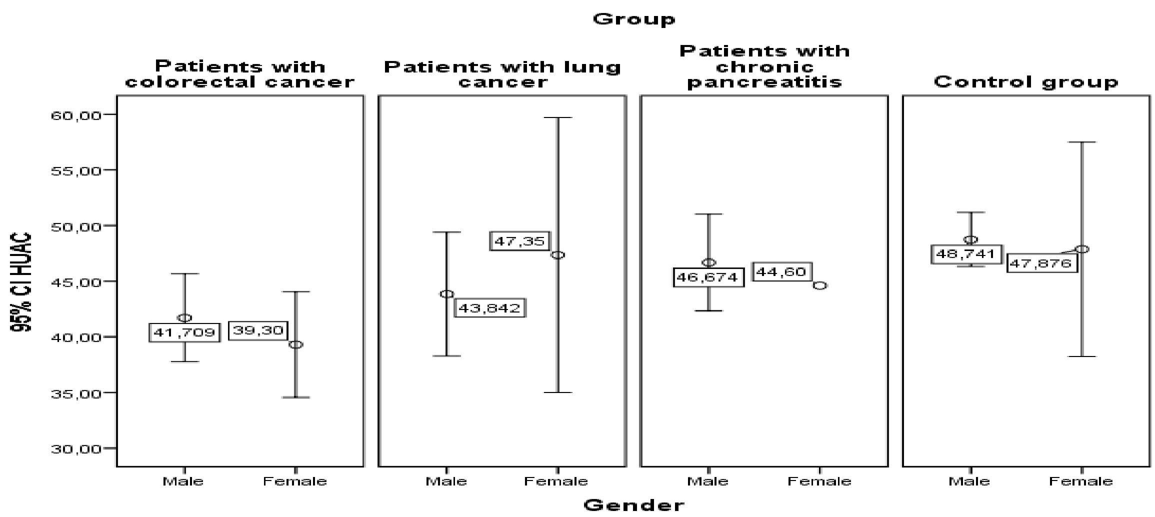

Fig. 30. Average HUAC values according to gender and study group

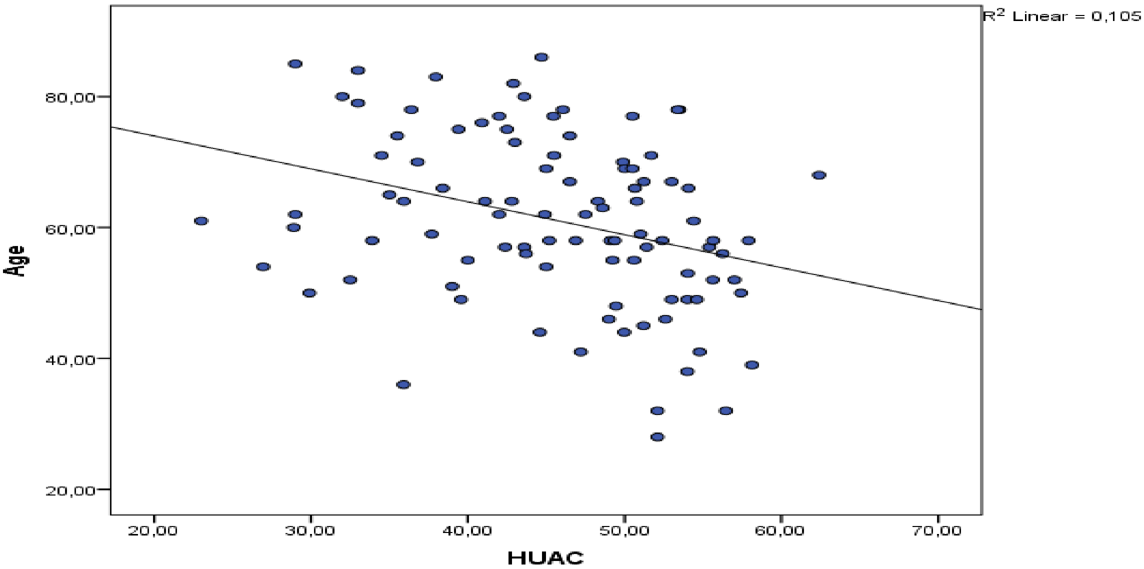

Fig. 31. Dependence between HUAC and age

In total, patients with available sarcopenia according to HUAC values in the entire sample were 24 people (25.0%), and no difference was found according to gender distribution, but a difference was found in relation to age (p<0.05) - patients with sarcopenia were more adults (respectively, 65.25 years for patients with sarcopenia to 59.71 years for patients without sarcopenia) (Fig. 32). Again, a logical result in view of what was commented on earlier.

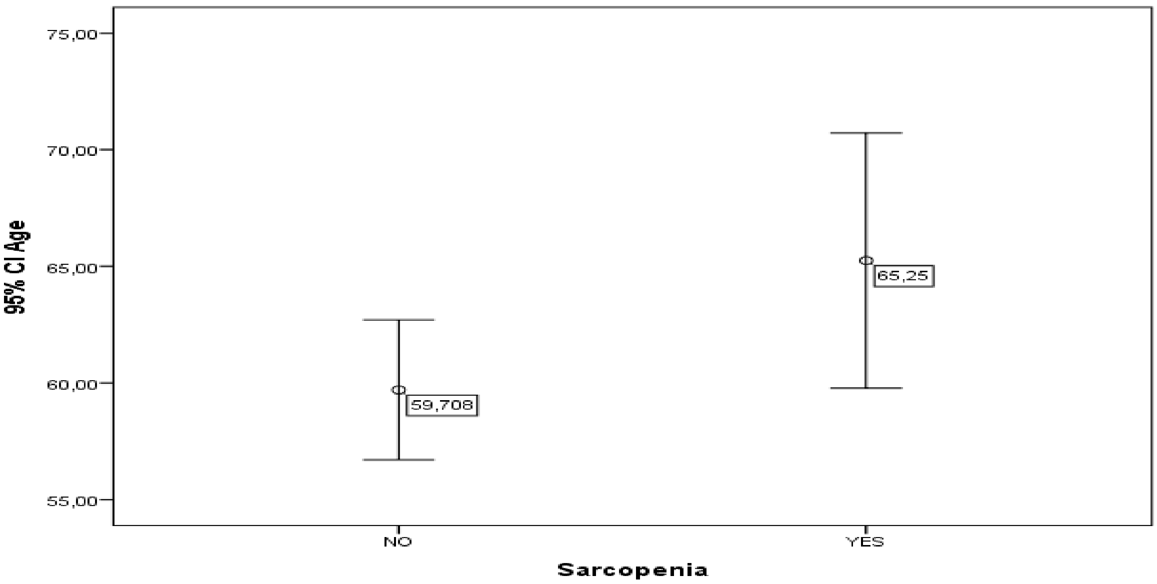

Fig. 32. Average age of patients with sarcopenia

Analyzing sarcopenia by gender and age of patients, shows that patients with sarcopenia are not only older, but there is an age predominance in women. According to our results, it can be said that in men, sarcopenia occurs at a slightly lower age compared to women (respectively, 64.1 years for men and 67.6 years for women) (p<0.05) (Fig. 33).

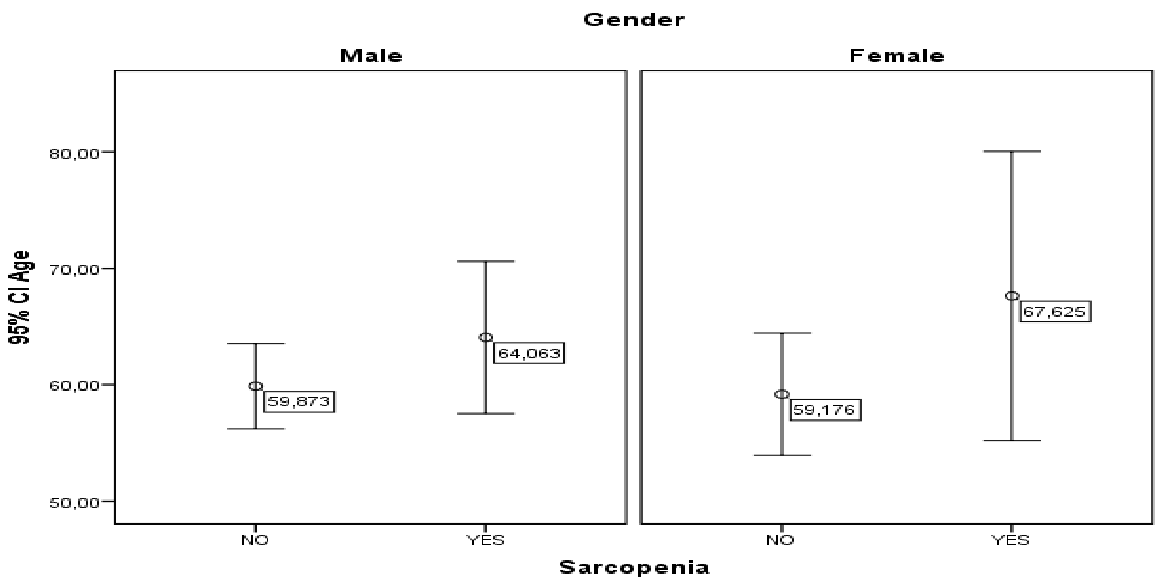

Fig. 33. Average age according to gender and the presence of sarcopenia

Examination of sarcopenia in the four studied groups showed the existence of a significant difference (p=0.029), with the highest relative share of sarcopenia in the group of patients with colorectal cancer (45.5 %), and the lowest share in the control group (13.9 %) (Fig. 34).

Performing a more detailed analysis showed that female gender was a risk factor for the presence of sarcopenia in patients with colorectal cancer (OR=2.1 (0.381-11.589); p<0.05), and male gender was a risk factor for the presence of sarcopenia in patients with lung carcinoma (OR=2.5 (0.370-16.888); p<0.05). In the control group, no difference was found between the patients with sarcopenia according to gender, and in the group of patients with chronic pancreatitis there were no women with sarcopenia (Fig. 35.).

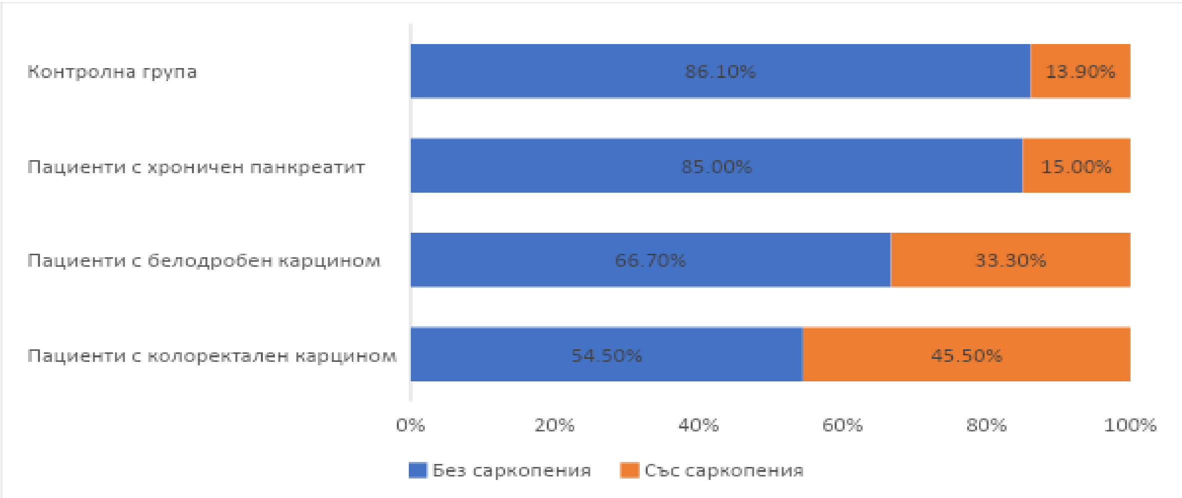

Fig. 34. Relative share of patients with sarcopenia in the studied groups

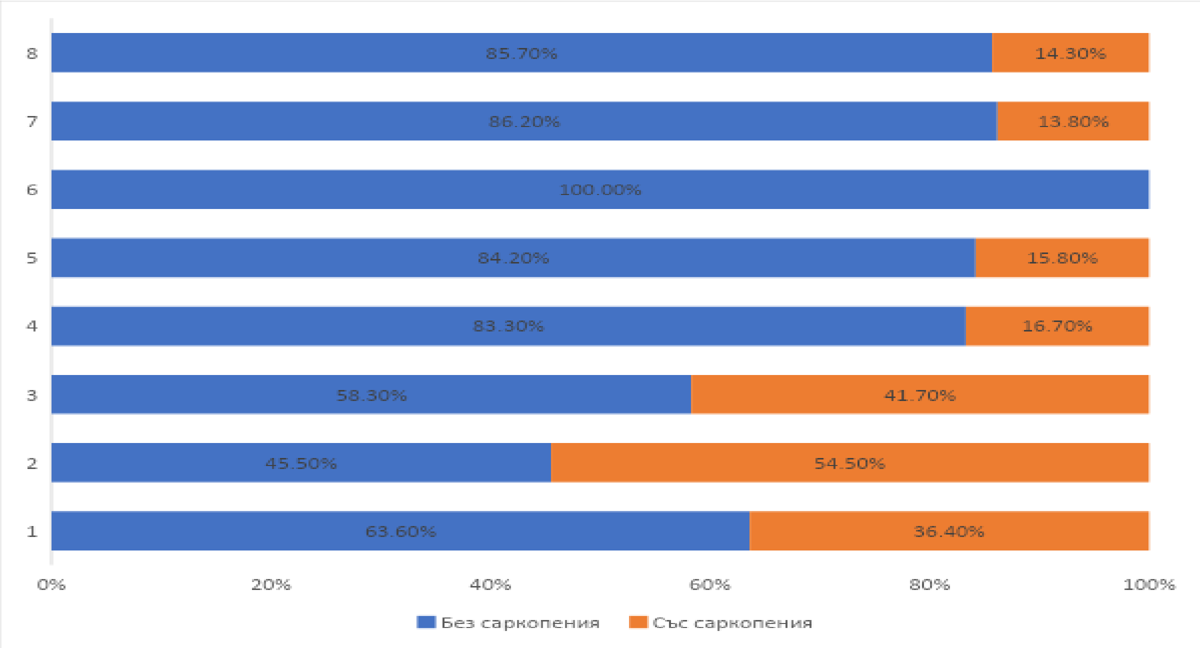

Fig. 35. Relative share of patients with sarcopenia according to gender in the studied groups

The second indicator studied is the Psoas Index (PI). The average value is 10.21 ± 2.84 cm2/m2 (5.74-18.30 cm2/m2) (Fig. 36). A significant difference was found in the average value of the indicator according to gender (p=0.021), with higher values observed in men (Fig. 37). A moderate correlation between female gender and Psoas Index (r=0.400; p=0.021) was also found.

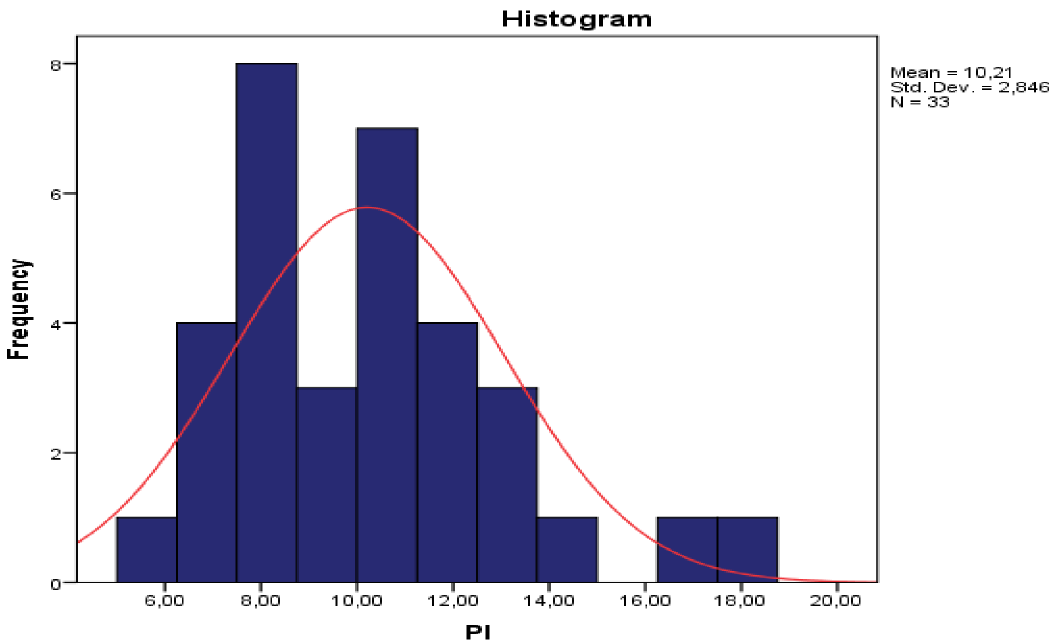

Fig. 36. Distribution of patients according to Psoas Index (PI)

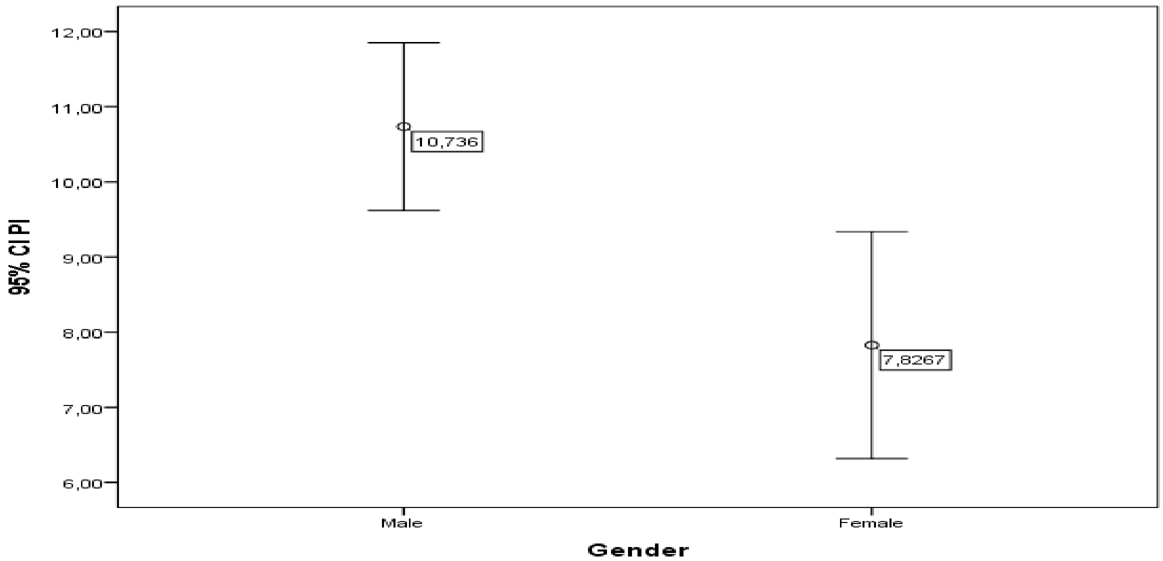

Fig. 37. Mean Psoas Index (PI) by gender

It is interesting that an inversely proportional moderate relationship between age and Psoas Index was found in men (r=-0.314; p=0.011). A relationship between age and Psoas Index in women was not found in the present study (Fig. 38).

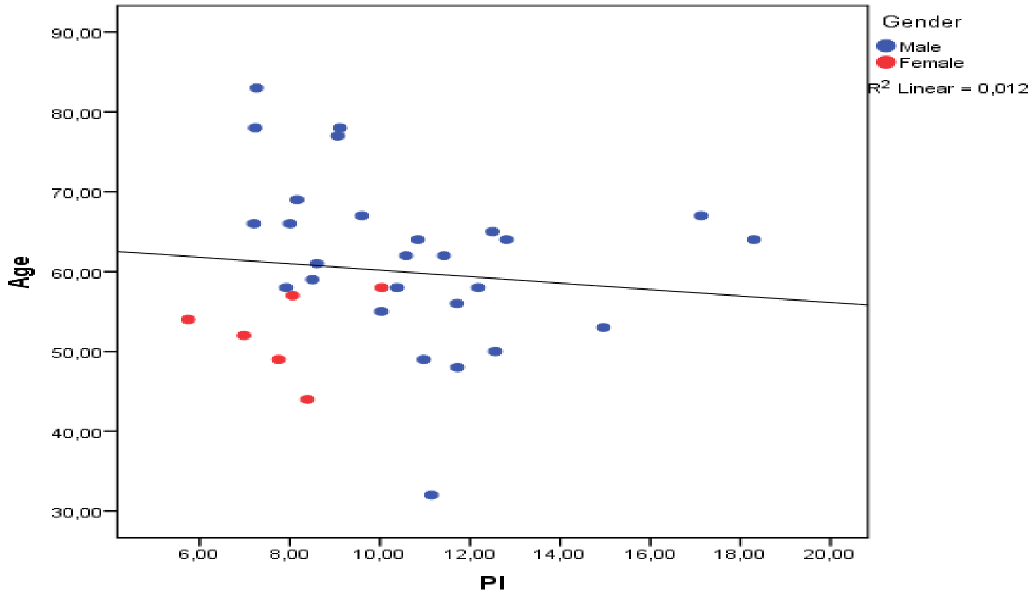

Fig. 38. Relationship between age and Psoas Index (PI) according to gender

No correlation was found between HUAC and Psoas Index (PI) in the studied group of patients.

4.3. To assess bone density with computed tomography using phantoms

In collaboration with the project "Clinical significance of abdominal visceral adipose tissue in patients with breathing disorders during sleep", headed by Prof. Dr. Diana Petkova Gospodinova-Valkova and in collaboration with the team of project FN21021 "An Innovative Method for Quality

Control of X-ray Systems", led by Prof. Kristina Bliznakova, a special in-house phantom was created in order to optimize the determination of bone density. The phantom serves as an objective benchmark by which the values of the Hunsfield units of bone density are normalized and The phantom is necessary because of the variation in voltage and current used during the scan, variations in which are automatically determined according to the patient's habitus by factory-set ionization dose optimization software.

The computer model for the phantom was created by one person in about 2 hours of work using Cinema4D software. Alternatively, other computer modeling programs such as Blender (completely free) or DesignSpark Mechanical (there is a free version) can be used. The phantom is a slightly bent carrier with embedded four test tubes filled respectively with distilled water and three solutions with reference concentrations of calcium chloride (Fig. 39).

The phantom serves as an objective benchmark against which Hunsfield bone density unit values are normalized and standardized across patients. The phantom is necessary because of the variation in voltage and current used during scanning, variations in which are automatically determined according to the patient's habitus by factory-set ionization dose optimization software.

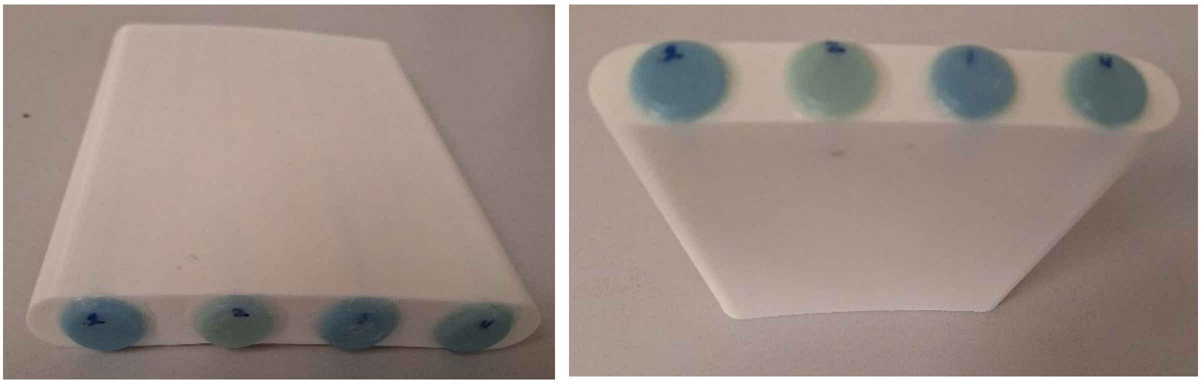

Fig. 39. Special in-house phantom to optimize bone density determination.

Fig. 40. The place of positioning of the phantom on the topogram

The phantom was printed from PLA filament on a professional Raise3D Pro3 Plus 3D printer with a large working area and the ability to print large models (Fig. 40).

There are more affordable models with a smaller print area that are satisfactory for printing the phantom and which, at the time of the model's production, cost between BGN 500 - 2000. The price of the PLA filament used for the phantom, model Raise3D Premium PLA White is 74.00 BGN per kilogram, and the material for the phantom itself is priced at 12.69 BGN. The calcium chloride used in the phantom tubes has a price of around 5-10 BGN per kilogram or 1-2 BGN per phantom. It took 49 hours and 14 minutes to print the phantom, and between 30 and 60 minutes to prepare the calcium chloride solutions and apply them to the phantom.

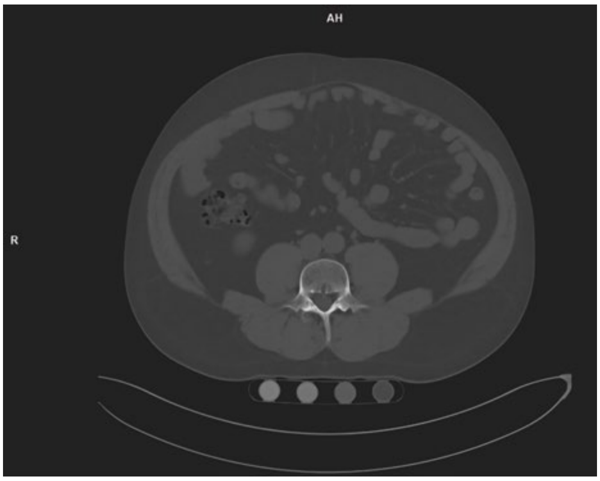

Fig. 41. Axial section of a native CT of the abdomen at the level of the body L3 with a specially created in-house phantom in order to optimize the determination of bone density containing four tubes filled with distilled water and three solutions with reference concentrations of calcium chloride, respectively. The phantom is positioned in the lumbar region.

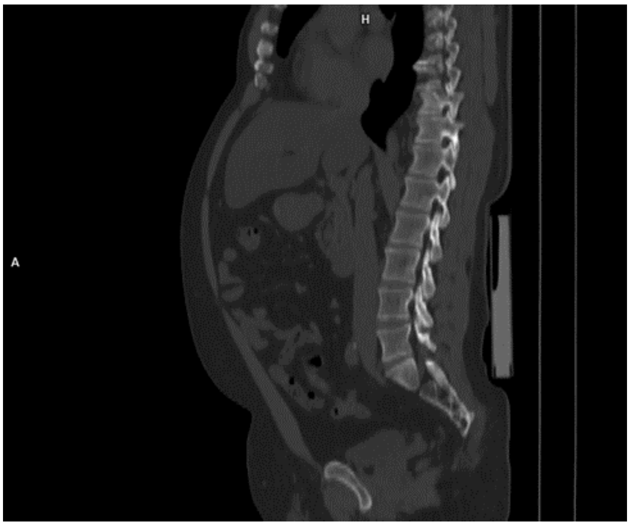

Fig. 42. Positioning of the sagittal slice phantom on native abdominal CT of the same patient.

4.4. To investigate and evaluate the relationship between bone density and subcutaneous and visceral adipose tissue

In all patients, the bone density of the body of L3 was examined and evaluated, and no significant difference was found in relation to the studied groups despite the variation of the values ($p>0.05$) (Fig. 43).

A significant difference was found according to the gender of the patients ($p<0.001$), with significantly lower bone density observed in women (respectively 40.52 HU for women and 51.54 HU for men) (Fig. 44). A moderate correlation was found between bone density and gender ($r=-0.454$; $p<0.001$), which shows that it decreases in women. This dependence and difference becomes even more visible when looking at the results according to gender and the studied groups ($p<0.001$) (Fig. 45), where women with chronic pancreatitis have the lowest bone density (27.0 HU), followed by women from the control group (36.37 HU).

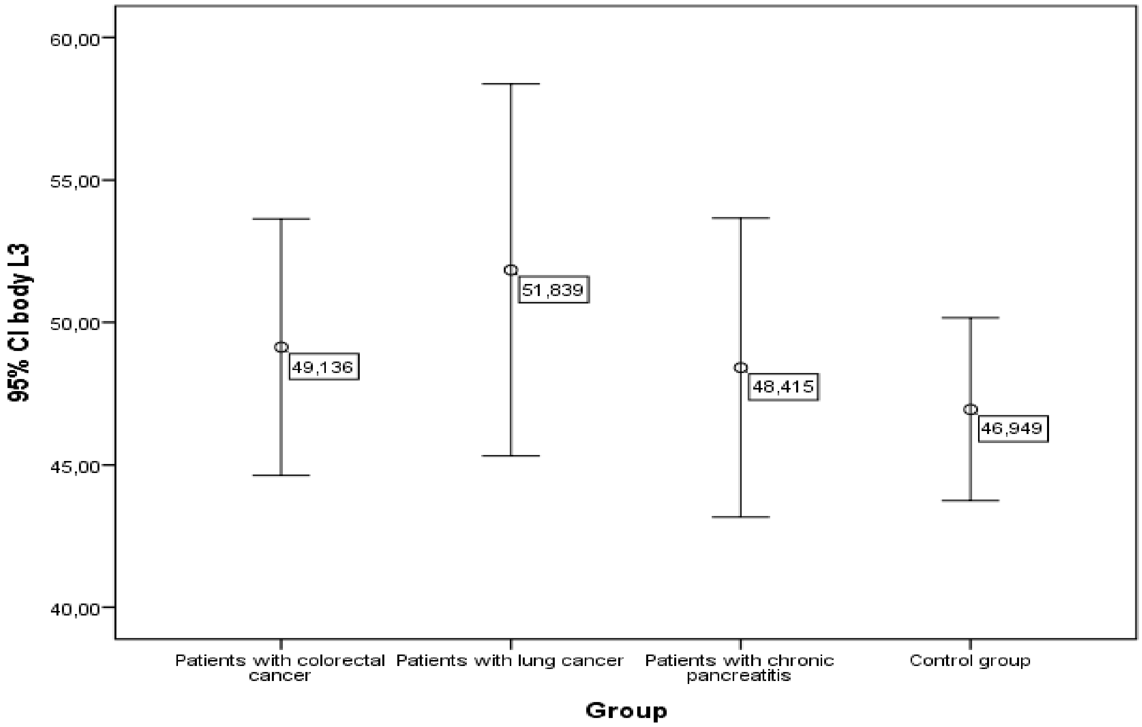

Fig. 43. Average value of the bone density of the body of L3 according to the studied groups

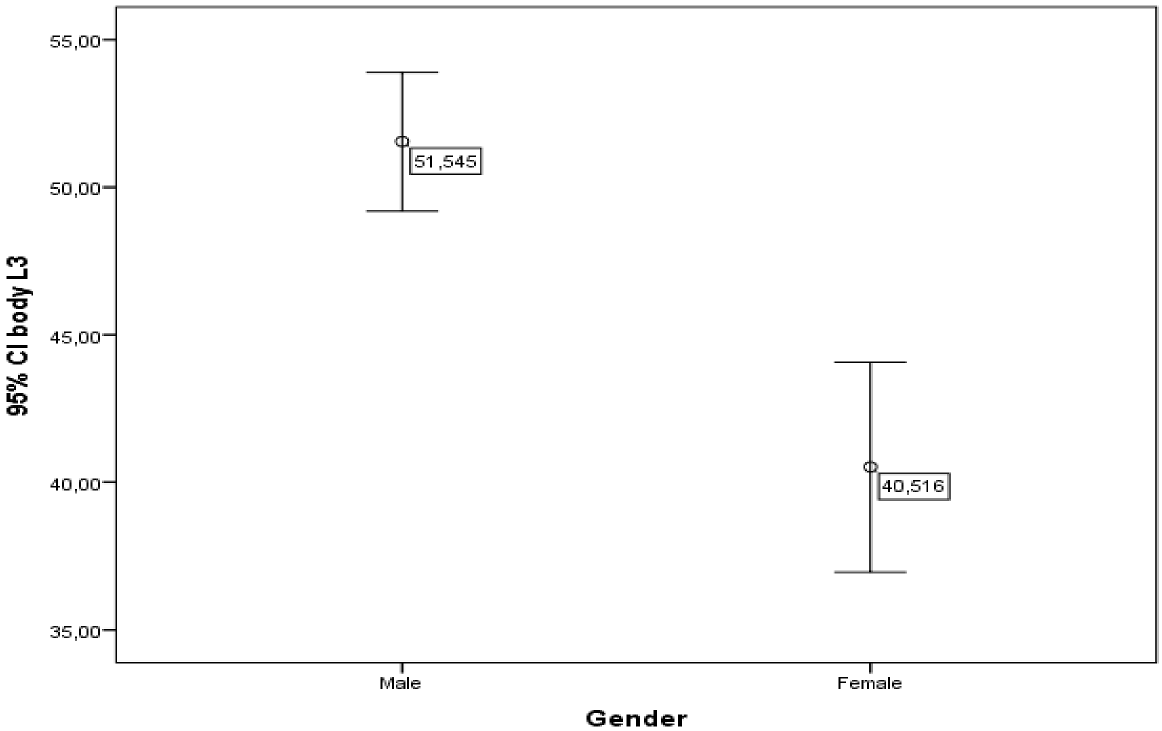

Fig. 44. Average values of body bone density at L3 by gender

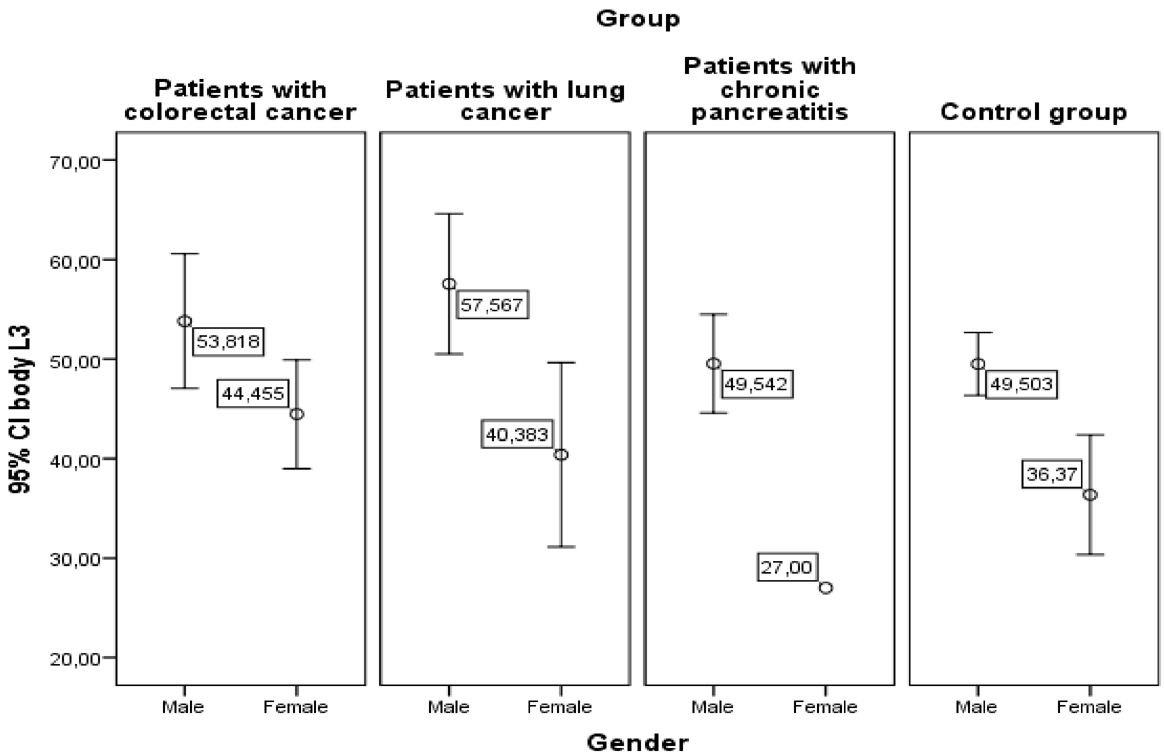

Fig. 45. Mean body bone density of L3 according to gender and study group

In the present sample, a directly proportional moderate relationship was found between L3 body bone density and age in both men (r=0.320; p=0.006) and women (r=0.392; p=0.05) (Fig. 46).

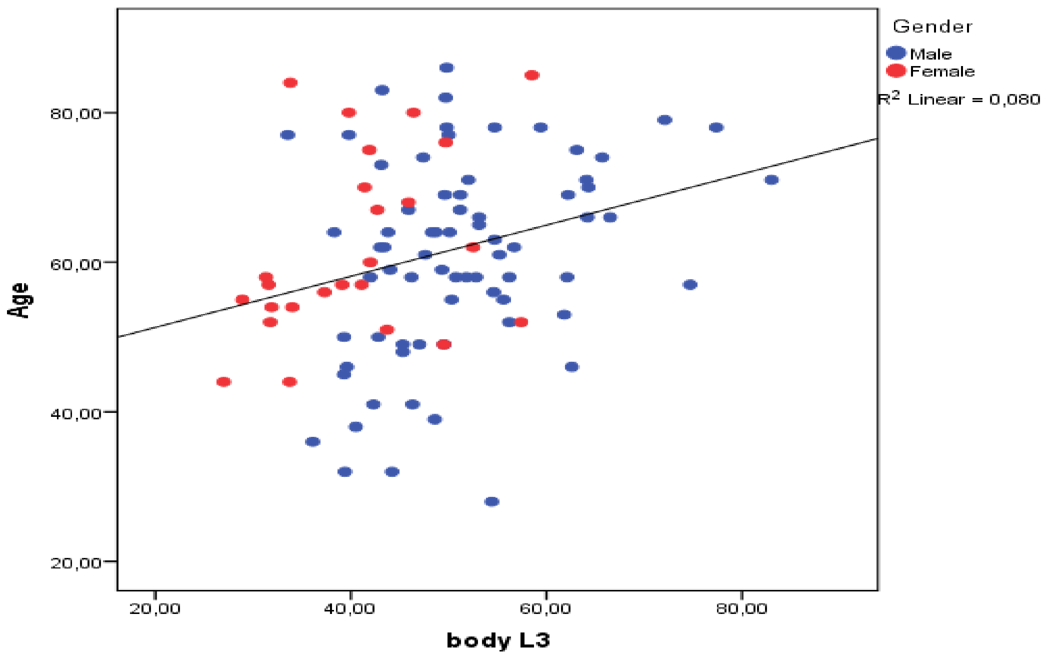

Fig. 46. Relationship between bone density of the body of L3 and age according to sex

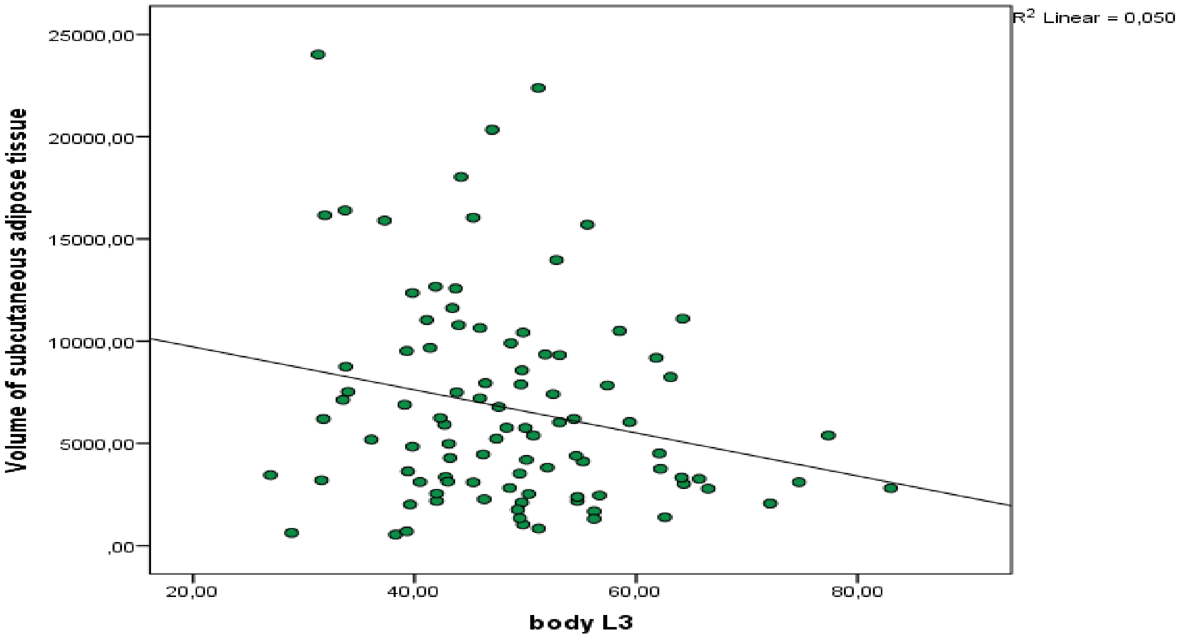

Fig. 47. Dependence between the bone density of the body of L3 and the volume of subcutaneous adipose tissue

Examination of the relationship between bone density and the volume of subcutaneous adipose tissue shows that there is an inversely proportional weak relationship between the two parameters (r=-0.224; p=0.028), which indicates that low bone density is associated with a greater volume of subcutaneous adipose tissue (Fig. 47).

This inverse relationship between the bone density of the body of L3 and the volume of subcutaneous adipose tissue was most pronounced in the group of patients with colorectal carcinoma (r=-0.488; p=0.021) (Fig. 48).

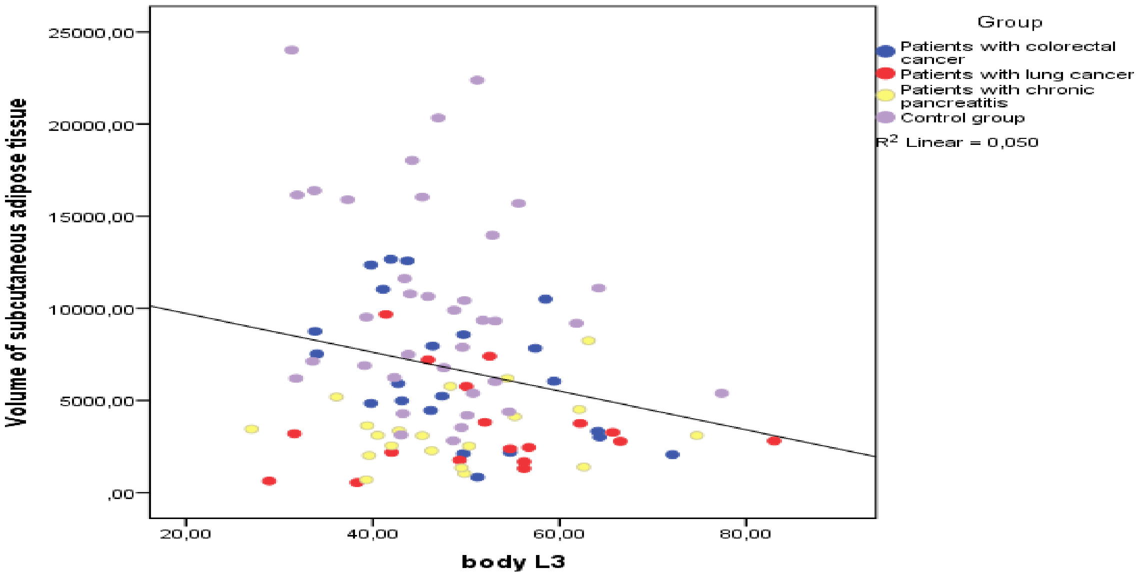

Fig. 48. Dependence between the bone density of the L3 body and the volume of subcutaneous adipose tissue according to the studied groups

An inversely proportional moderate correlation was found between L3 body bone density and mean subcutaneous fat density in women (r=-0.409; p=0.043) (Fig. 49), but not in men.

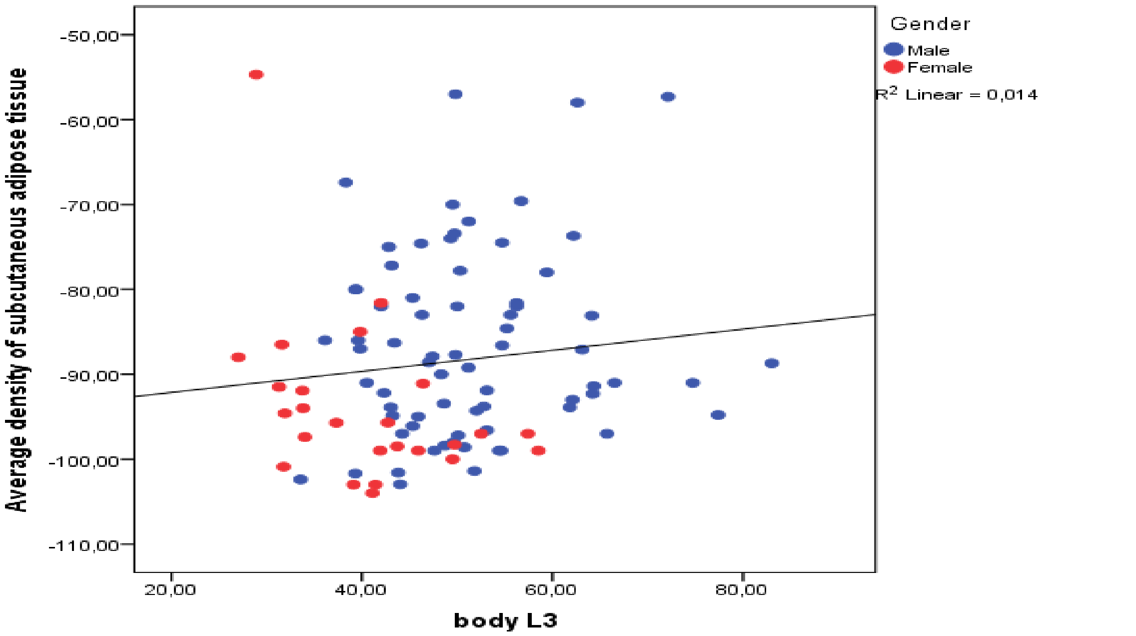

Fig. 49. Relationship between L3 body bone density and mean subcutaneous fat density by gender

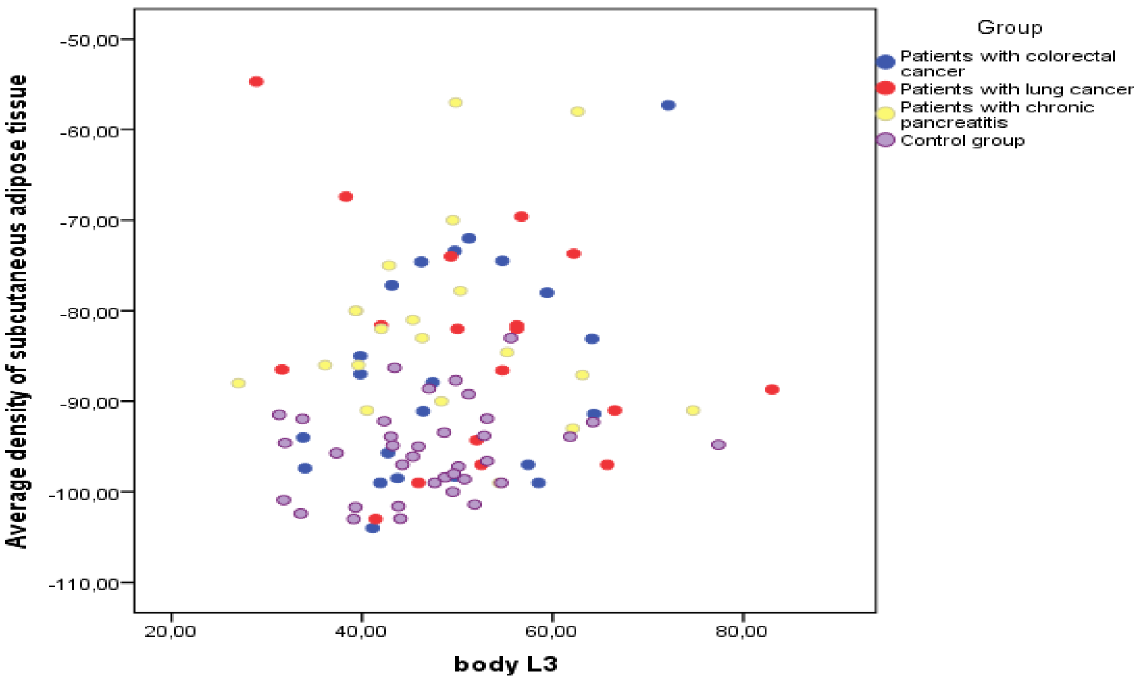

Fig. 50. Dependence between the bone density of the body of L3 and the average density of subcutaneous fat according to the studied groups

In contrast to the volume of subcutaneous adipose tissue, when examining the relationship between mean subcutaneous adipose tissue density and L3 body bone density, some significant differences were observed in patients from the four study groups. In the group of patients with colorectal carcinoma, a directly proportional relationship was established between the average density of subcutaneous fat tissue and the bone density of the L3 body (r=0.462; p=0.030). In the group of patients with lung cancer, an inversely proportional moderate relationship was established between the two indicators (r=-0.308; p=0.021). While in patients with chronic pancreatitis and the control group, no relationship was established between the average density of subcutaneous fat tissue and the bone density of the L3 body (Fig. 50).

No correlation was found between the volume and mean density of visceral adipose tissue and the bone density of the L3 body.

A weak inverse correlation was found between the area of subcutaneous adipose tissue at the L3-L4 level and bone density of the L3 body (r=-0.176; p=0.086) (Fig. 51), which was mainly due to female sex, but not found such a relationship with the area of visceral adipose tissue at the L3-L4 level.

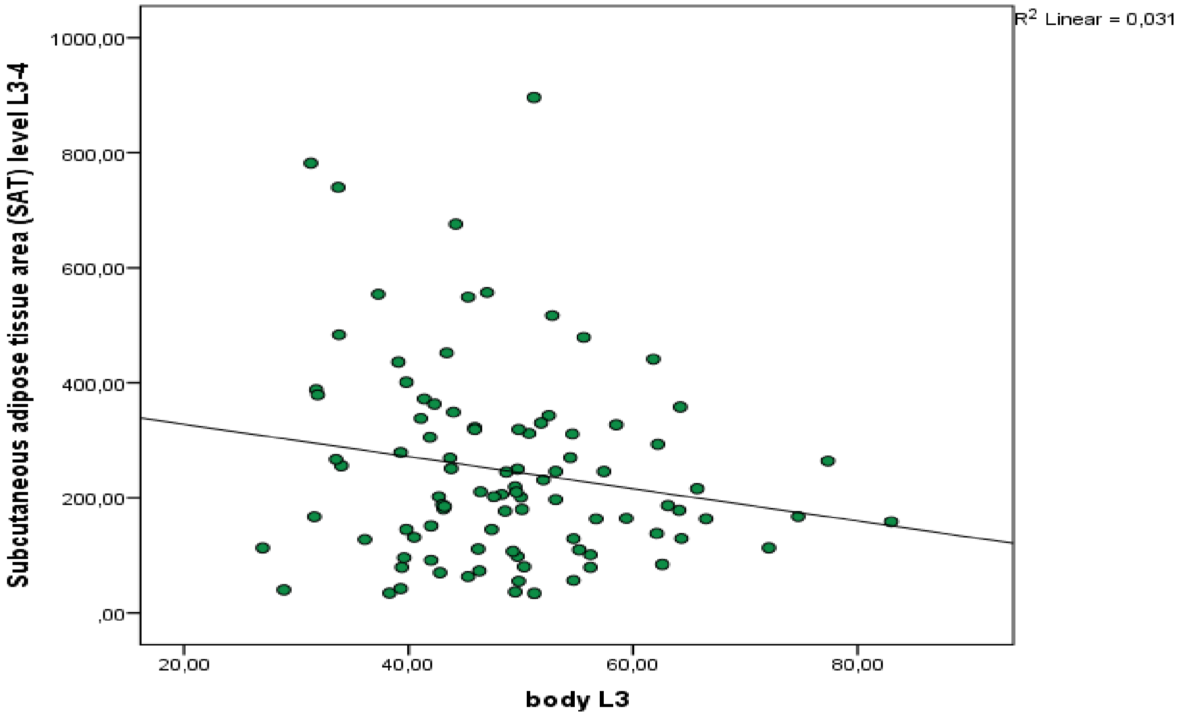

Fig. 51. Relationship between the area of subcutaneous adipose tissue at the level of L3-L4 and the bone density of the body of L3

A weak inverse correlation was also found between the area of subcutaneous adipose tissue at the L4-L5 level and the bone density of the body at L3 (r=-0.187; p=0.067) (Fig. 52), and here also the dependence was due to the female gender. No such correlation was found with the area of visceral adipose tissue at the L4-L5 level.

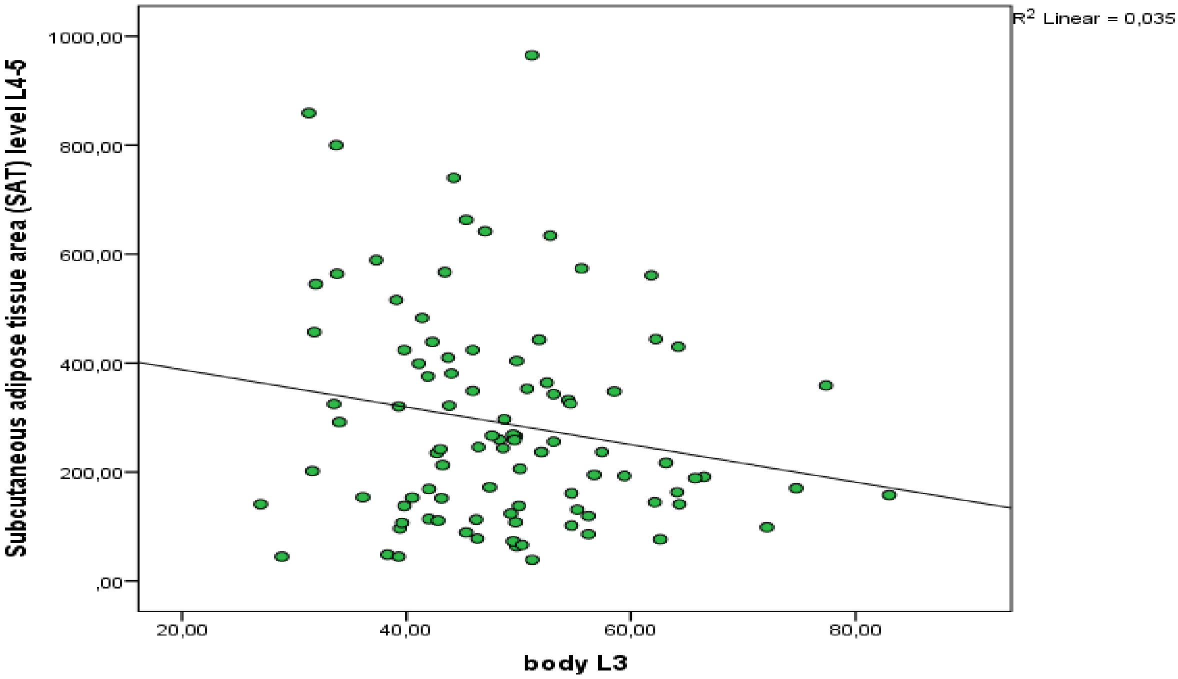

Fig. 52. Relationship between the area of subcutaneous adipose tissue at the level of L4-L5 and the bone density of the body of L3

4.5. To investigate and assess the relationship between CT indices of subcutaneous and visceral adipose tissue, bone density and sarcopenia

Examination of the volume of subcutaneous adipose tissue according to the presence of sarcopenia showed no significant difference. But a more detailed analysis showed that in patients with sarcopenia, higher values of the volume of subcutaneous adipose tissue were found in women (9824.08 cm3 vs. 8814.34cm3) and lower in men (5245.36 cm3 vs. 6016.25 cm3), observing significant difference in the volume of subcutaneous adipose tissue between both sexes in the group of patients with sarcopenia ($p<0.01$), but also between men and women in both groups ($p<0.05$) (Fig. 53).

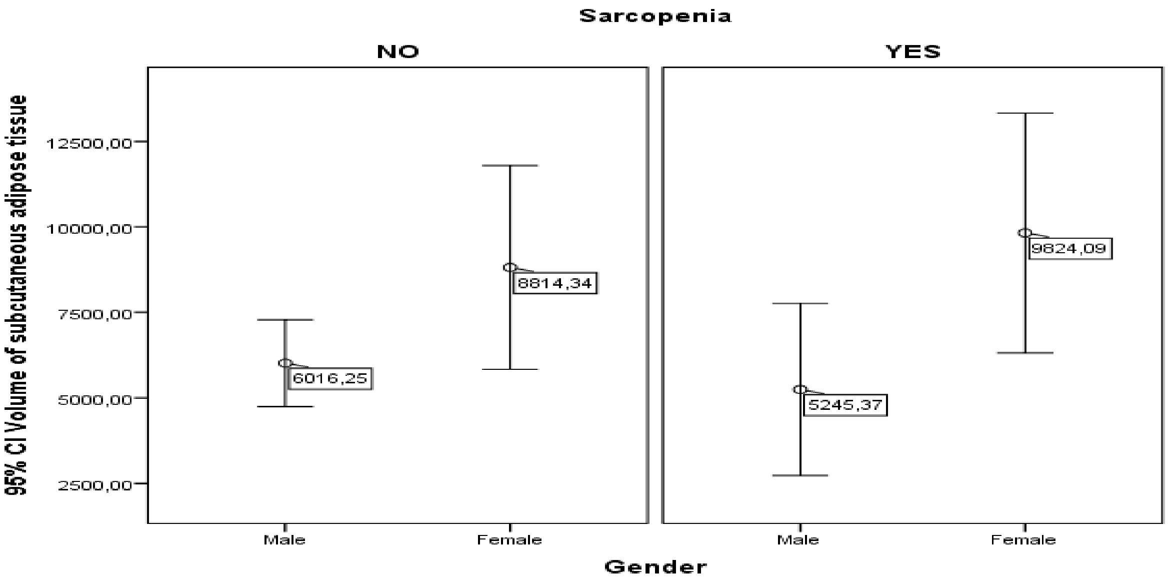

Fig. 53. Average values of the volume of subcutaneous adipose tissue according to the presence of sarcopenia and gender

A significant difference in the volume of subcutaneous adipose tissue was also found in relation to the patients with sarcopenia in the studied groups (p<0.001), where the patients with lung carcinoma (2212.58 cm3) had the smallest volume of subcutaneous adipose tissue (2212.58 cm3), and the most large patients of the control group (11 996.57 cm3). (Fig. 54).

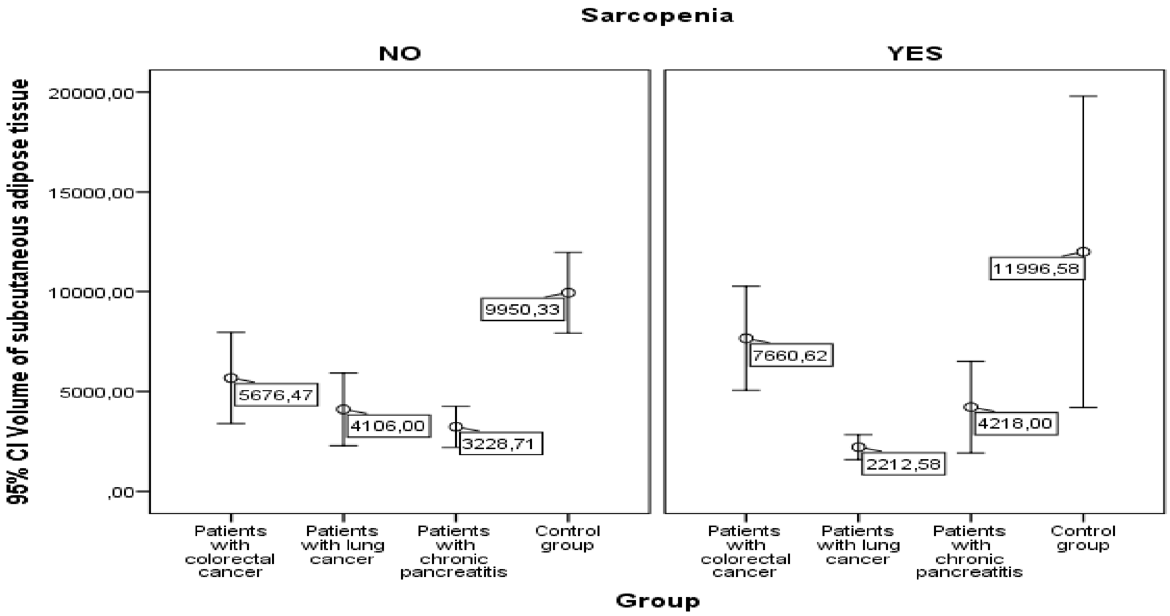

Fig. 54. Average values of the volume of subcutaneous adipose tissue according to the presence of sarcopenia and the studied group

A difference was also found in the volume of subcutaneous adipose tissue in the studied groups between patients with and without sarcopenia (p<0.01), where significantly higher values of the volume of subcutaneous adipose tissue were found in patients with lung cancer than in the group of those without sarcopenia. (respectively 4106 cm3 to 2212.58 cm3) (Fig. 55).

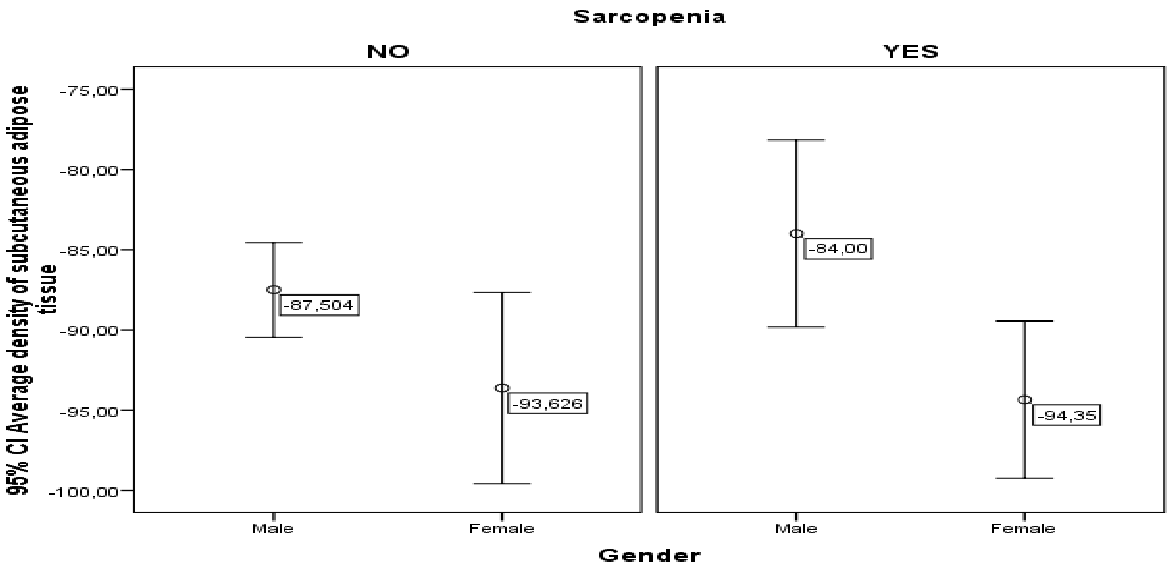

Fig. 55. Mean values of the density of subcutaneous adipose tissue according to the presence of sarcopenia and gender

In patients with sarcopenia, lower values of the mean density of subcutaneous fat tissue were found in women (-94.35 HU to -93.63 HU) and higher in men (-84.0 HU to -87.50 HU), with a significant difference in the average density of subcutaneous adipose tissue between both sexes in the group of patients with sarcopenia ($p<0.01$), but also between men and women in both groups ($p<0.05$) (Fig. 56). In contrast to the volume of subcutaneous adipose tissue, no significant difference was found for density in relation to sarcopenia and the studied groups despite the variation in values (Fig. 56).

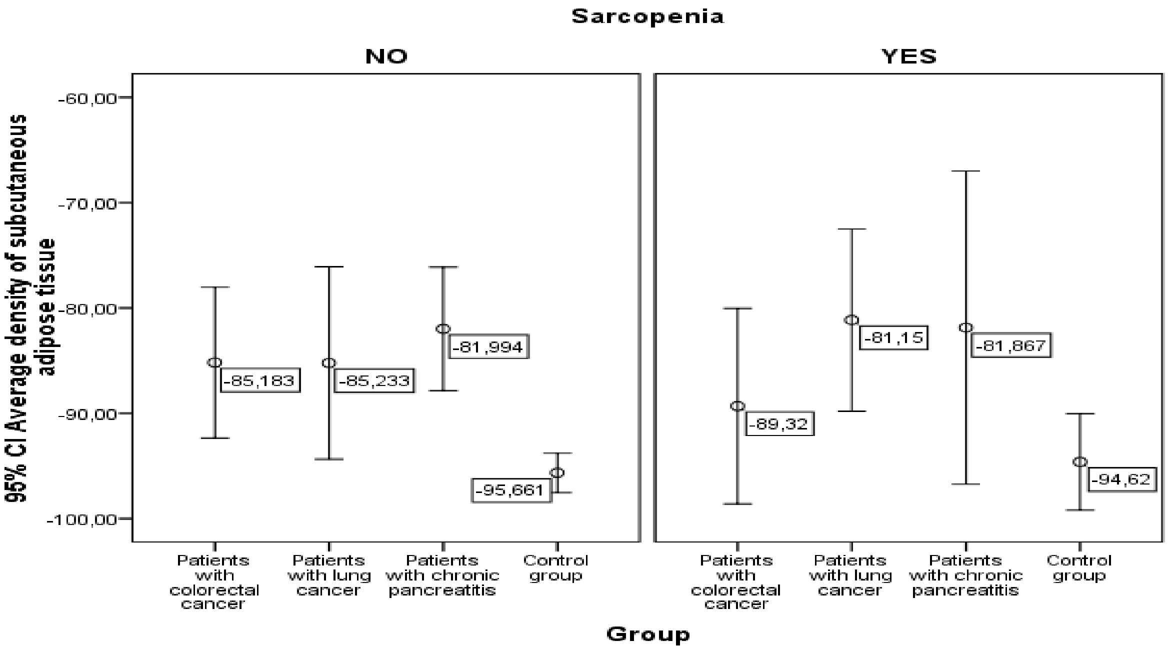

Fig. 56. Average values of the density of subcutaneous adipose tissue according to the presence of sarcopenia and the studied group

In patients with sarcopenia, higher values of the volume of visceral adipose tissue were found in both women (4864.45 cm3 vs. 3642.92 cm3) and in men (5497.85cm3 vs. 5198.25cm3), and a significant difference was observed in the volume of subcutaneous adipose tissue between both sexes in the group of patients with sarcopenia ($p<0.05$), but also between men and women in both groups ($p<0.05$) (Fig. 57).

A significant difference in the volume of visceral adipose tissue was also found in relation to the patients with sarcopenia in the studied groups ($p<0.001$), where the patients with lung carcinoma had the smallest volume of subcutaneous adipose tissue (3085.80 cm3), and the most large patients from the control group (10621.74 cm3). (Fig. 58). A difference was also found in the volume of subcutaneous adipose tissue in the studied groups between patients with and without sarcopenia ($p<0.01$), where patients without sarcopenia had lower values of the volume of visceral adipose tissue (Fig. 58).

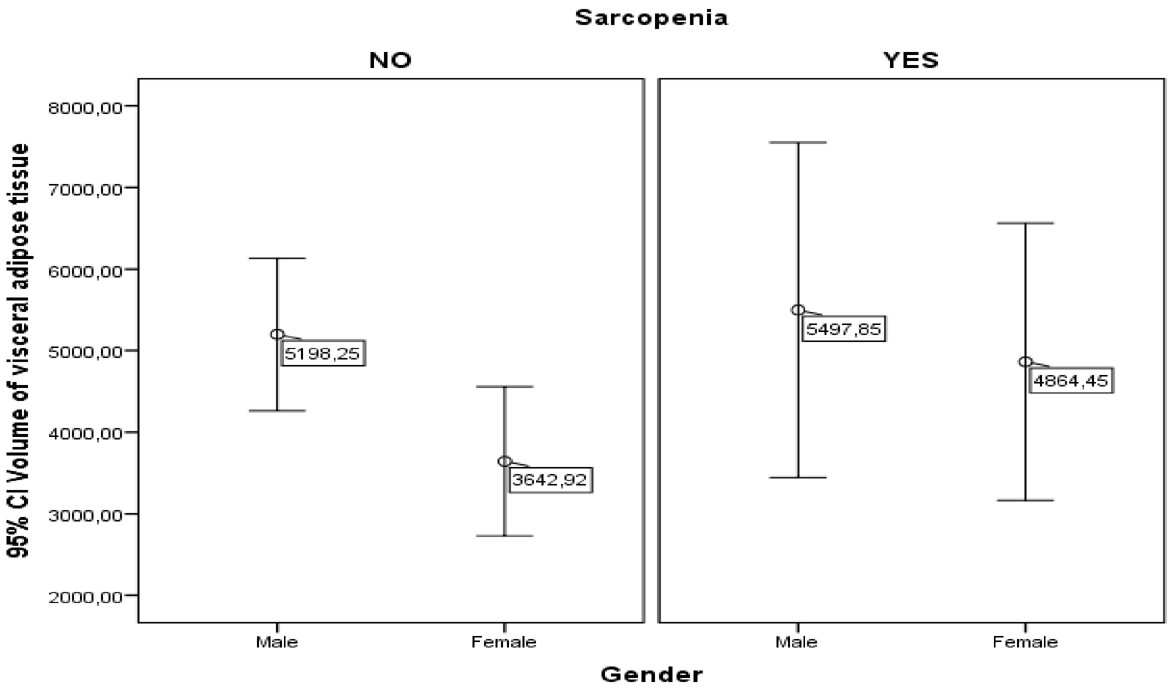

Fig. 57. Average values of the volume of subcutaneous adipose tissue according to the presence of sarcopenia and gender

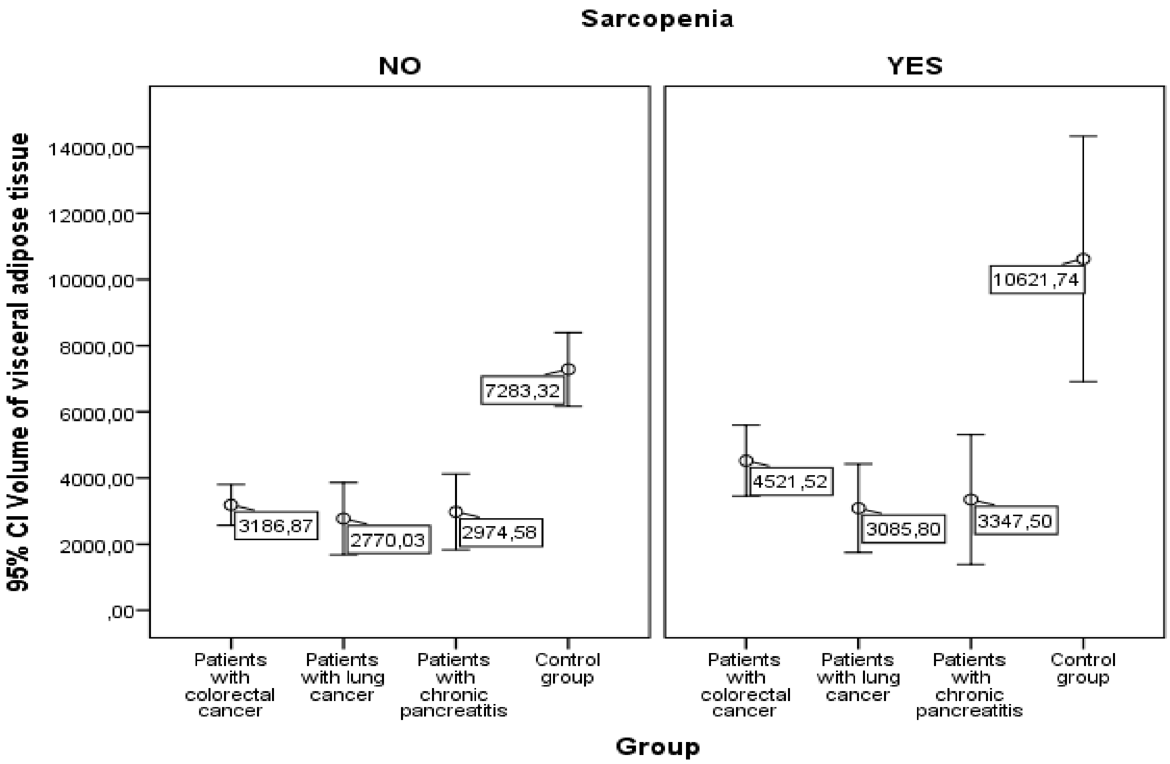

Fig. 58. Mean values of the volume of visceral adipose tissue according to the presence of sarcopenia and the studied group

In contrast to visceral adipose tissue volume, density did not show a significant difference in relation to sarcopenia according to gender and study groups despite varying values (Fig. 59 and Fig. 60).

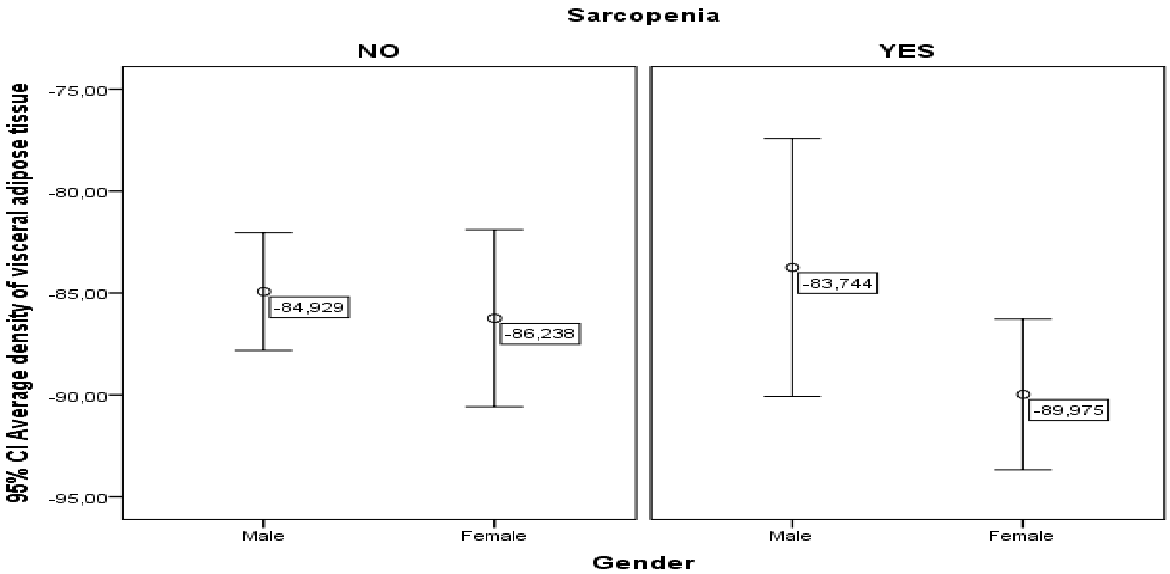

Fig. 59. Mean values of visceral adipose tissue density according to the presence of sarcopenia and sex

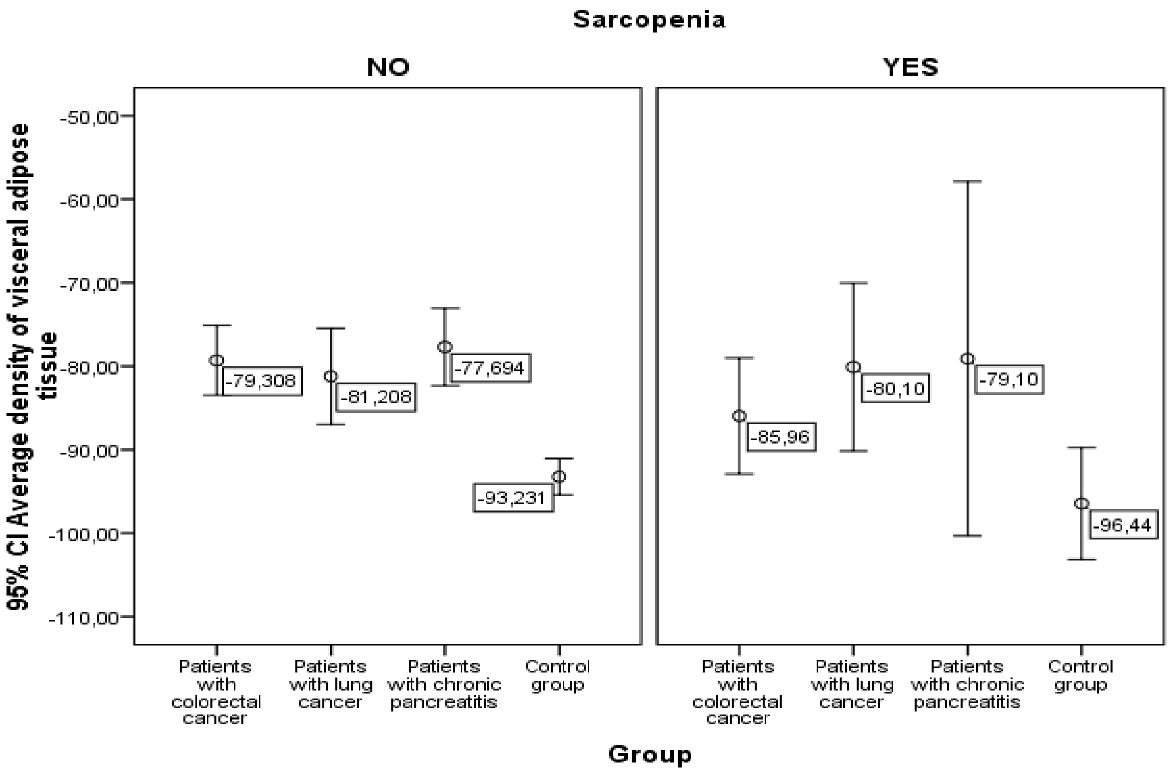

Fig. 60. Mean values of the density of visceral adipose tissue according to the presence of sarcopenia and the studied group

No correlation was found between the HUAC index and the volume and density of subcutaneous and visceral adipose tissue.

Although no significant difference was found, an interesting result was that patients with sarcopenia had a higher bone density per body at L3 (Fig. 61.)

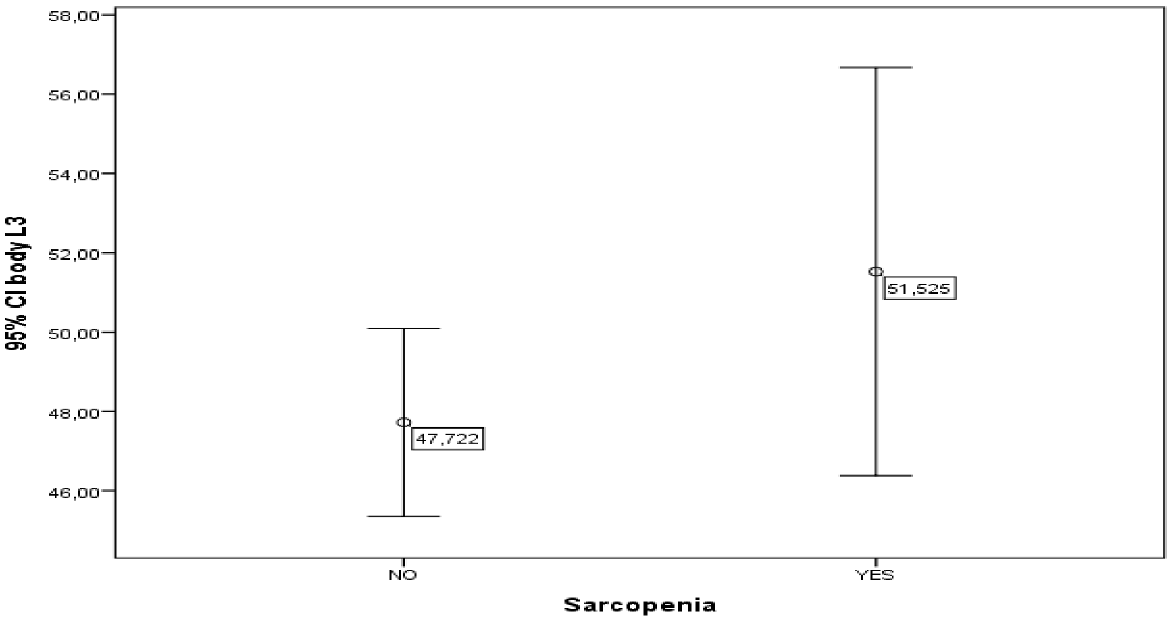

Fig. 61. Average value of bone density body at L3 according to the presence of sarcopenia

No relationship was found between L3 body bone density and the presence of sarcopenia.

On the other hand, a more detailed analysis of body bone density at L3 according to the presence of sarcopenia and gender shows that there is a significant difference between men and women ($p<0.05$), who have higher bone density in the group of those with sarcopenia (Fig. 62).

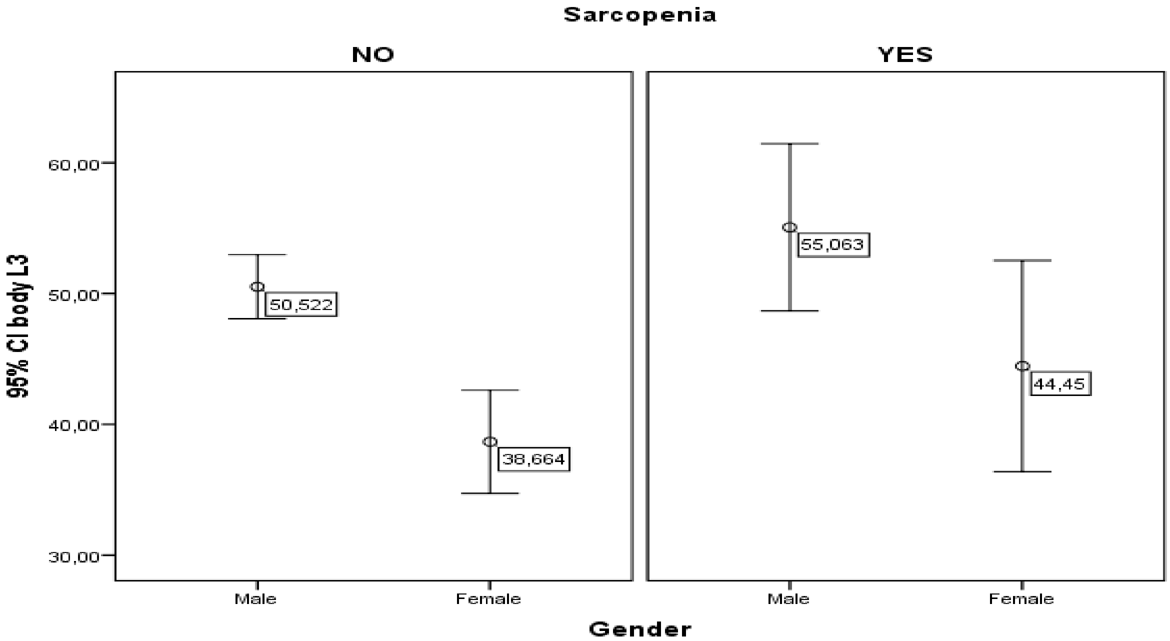

Fig. 62. Mean L3 body bone density values according to the presence of sarcopenia and sex

A significant difference was found in the average values of bone density of the L3 body according to the presence of sarcopenia and the studied groups (p<0.01), with higher levels of bone density observed in patients with colorectal carcinoma and lung carcinoma with sarcopenia (respectively 52.49 HU and 58.95 HU) compared to those without sarcopenia, while in patients with chronic pancreatitis and the control group, the bone density of those with sarcopenia was lower compared to those without (Fig. 63).

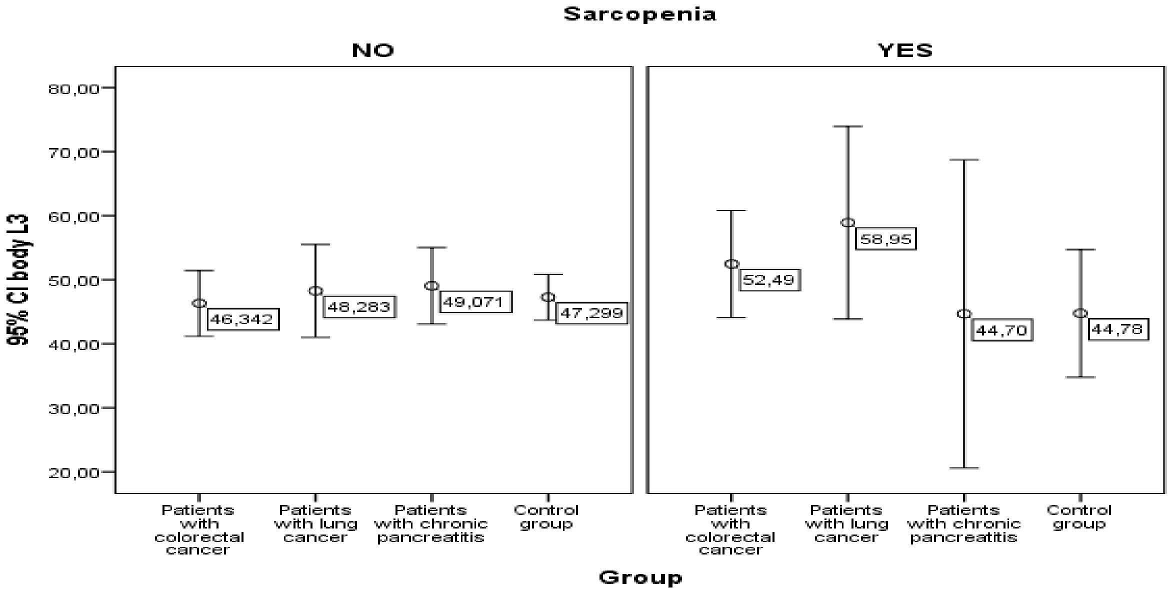

Fig. 63. Mean values of bone density of the L3 body according to the presence of sarcopenia and the study group

4.6. To investigate the influence of the inflammatory process on indicators of subcutaneous and visceral adipose tissue, bone density and sarcopenia

For the investigation of the inflammatory process, the levels of leukocytes, CRP and ESR were analyzed.

The average level of leukocytes was 13.76 ± 12.07, with the minimum value being 3.92 and the maximum 87.20. No significant difference was found in the levels of leukocytes according to the studied group of patients. No association was found between leukocyte levels and indicators of subcutaneous and visceral adipose tissue, bone density and sarcopenia.

The examination of the mean levels of CRP showed that the patients were characterized by the presence of an inflammatory process, with the mean value of the indicator being 68.66 mg/L ± 80.48 mg/L and varying between 1.66 mg/L and 270.12 mg/L. Only three patients had CRP levels below 5 mg/L. No significant difference was found in CRP levels according to the studied patient group. Examination of the relationship between CRP levels and visceral adipose tissue volume showed a weak to moderate directly proportional relationship (r=0.286; p<0.05), indicating that increased visceral adipose tissue volume may be associated with the onset of an inflammatory process (Fig. 64).

Although no significant difference was found, it can be said that patients with sarcopenia had higher levels of CRP (Fig. 65).

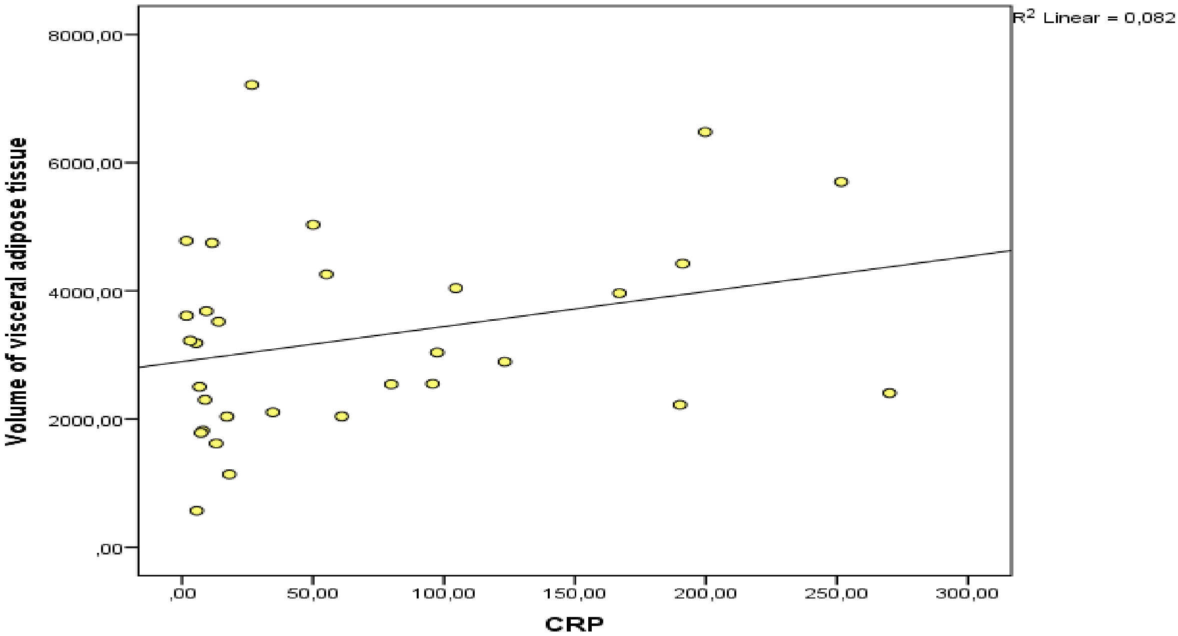

Fig. 64. Relationship between CRP levels and visceral adipose tissue volume

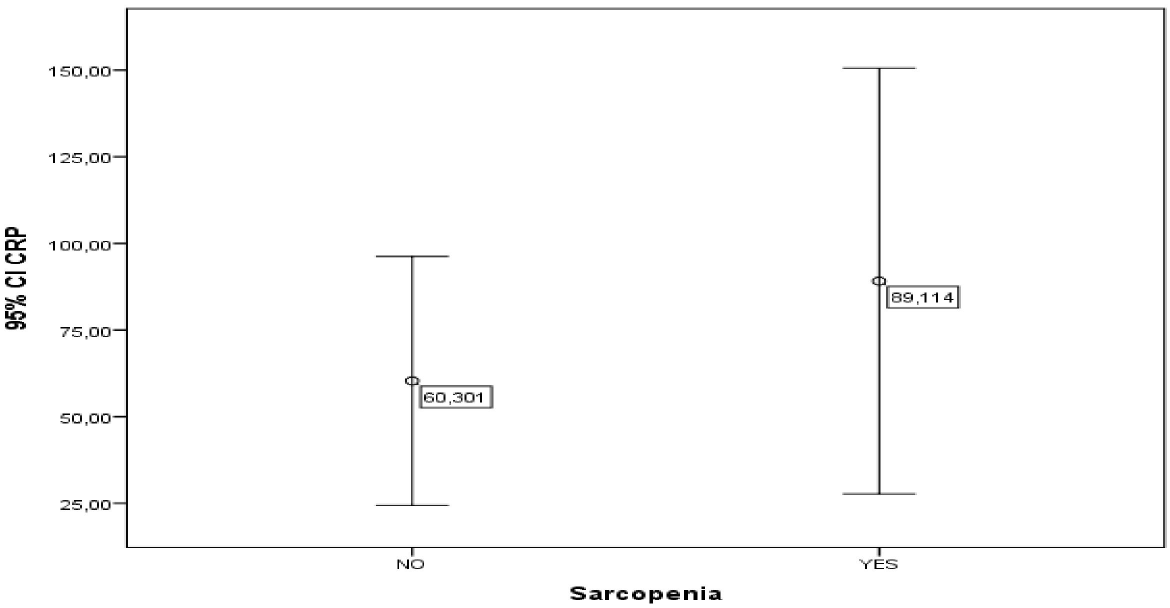

Fig. 65. Mean CRP levels according to the presence of sarcopenia

A directly proportional weak relationship between serum CRP levels and the area of visceral adipose tissue at the L3-4 level was also established (r=0.231; p<0.05) (Fig. 66).

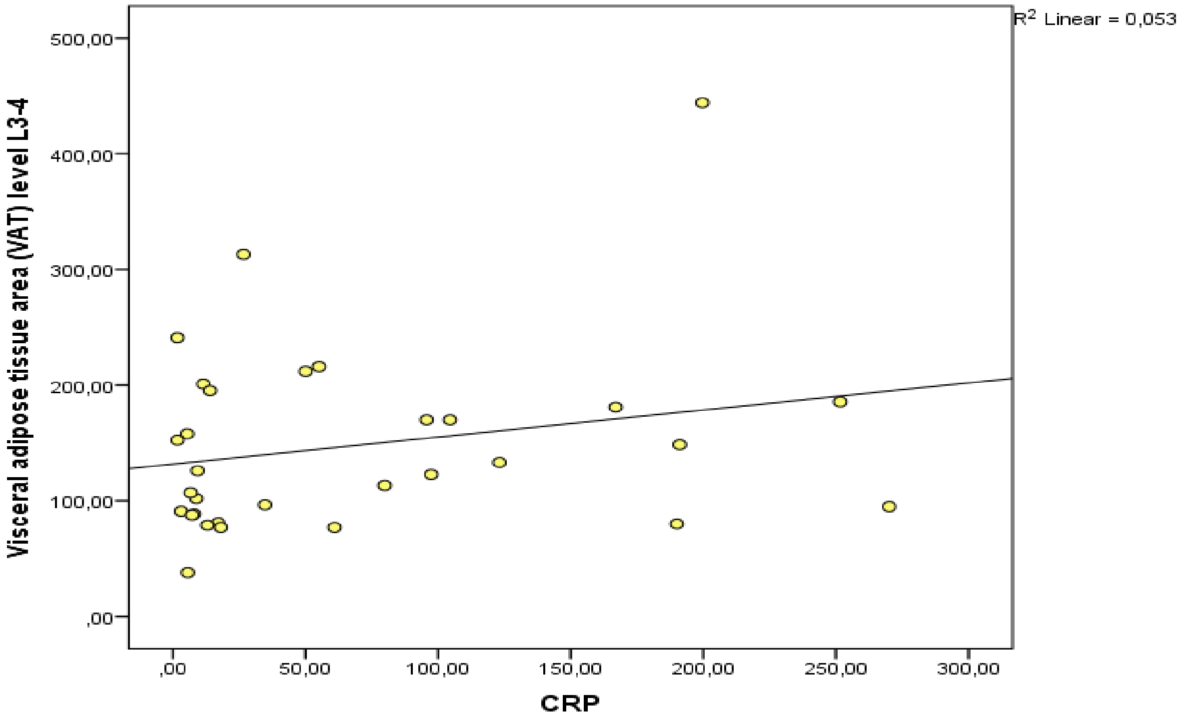

Fig. 66. Relationship between CRP levels and the area of visceral adipose tissue at the L3-4 level

A directly proportional moderate relationship between serum CRP levels and the area of visceral adipose tissue at the L4-5 level was also found ($r=0.390$; $p<0.05$) (Fig. 67).

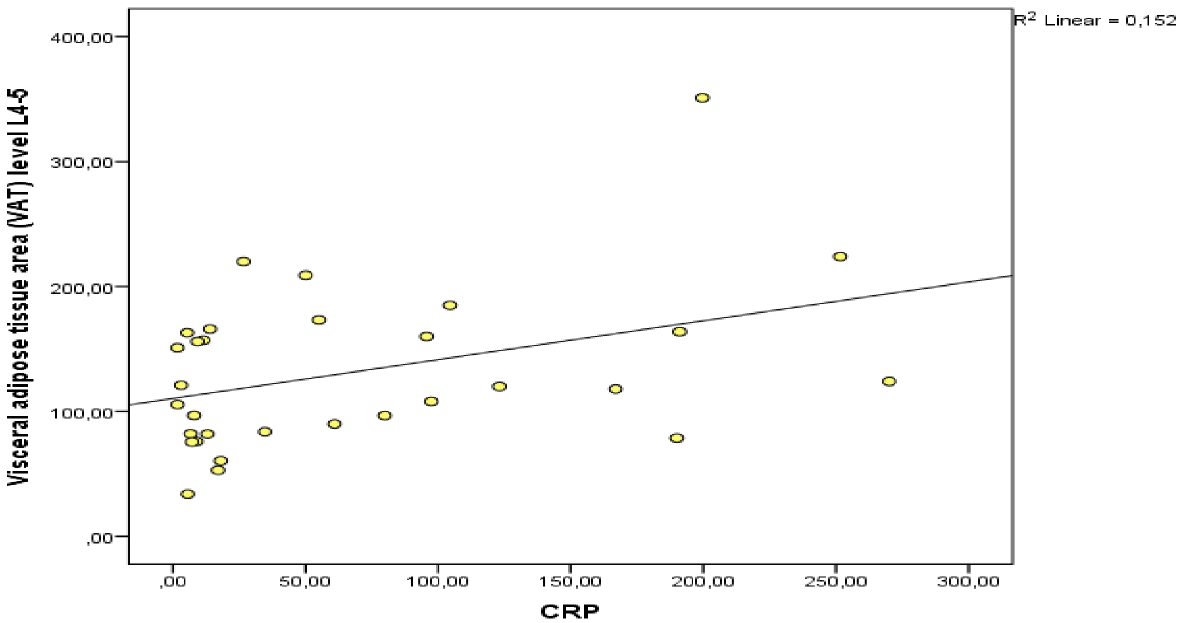

Fig. 67. Relationship between CRP levels and the area of visceral adipose tissue at the L4-5 level

The results of the analyzes showed that the inflammatory process measured by CRP levels was associated with visceral adipose tissue assessment indicators and showed that increased visceral adipose tissue volume and area were associated with the presence of an inflammatory process.

The third indicator of inflammation used in the present study was serum ESR levels. The average value of the indicator is 64.21 mm/h ± 32.75 mm/h and varies between 2 and 120 mm/h. No significant difference was found in the levels of ESR according to the studied group of patients, as well as according to the presence of sarcopenia.

The study of the relationship between the ESR and the indicators of bone density of the body L3 showed the presence of an inversely proportional moderate dependence ($r=-0.304$; $p<0.05$), indicating that the inflammatory process correlates with decreased bone density (Fig. 68).

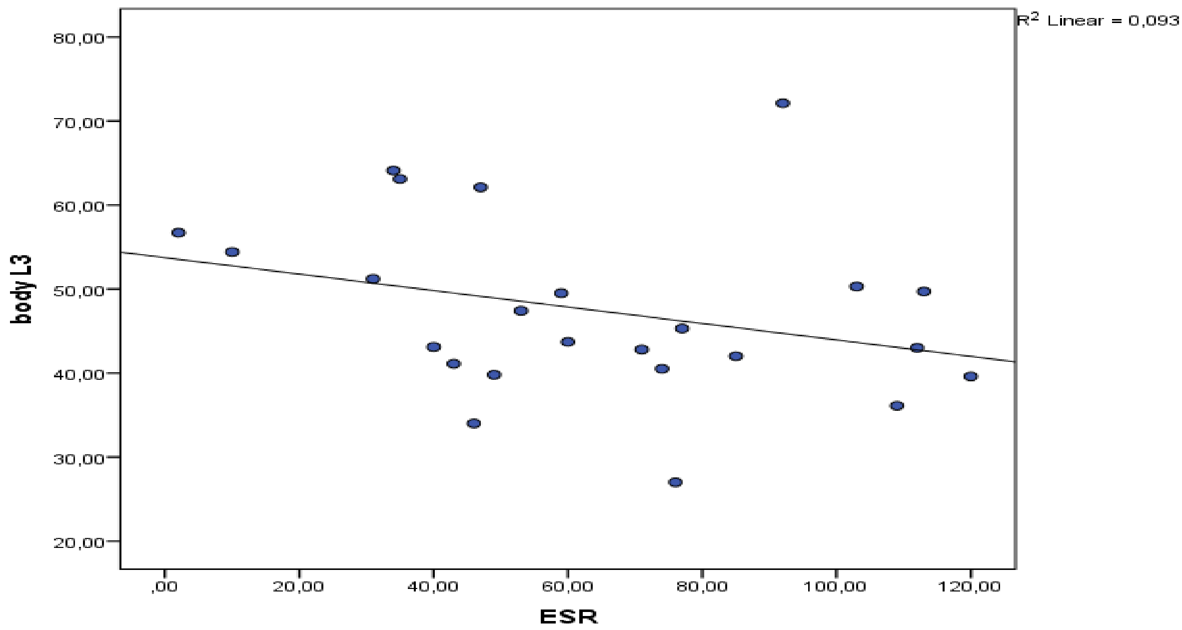

Fig. 68. Relationship between ESR levels and bone density measured at body L3

A weak, tending to moderate inverse correlation was also found between serum ESR levels and the area of subcutaneous fat tissue measured at the level of L3-4 ($r=-0.283$; $p<0.05$) and L4-5 ($r=-0.274$; $p<0.05$) (Fig. 69 and Fig. 70)

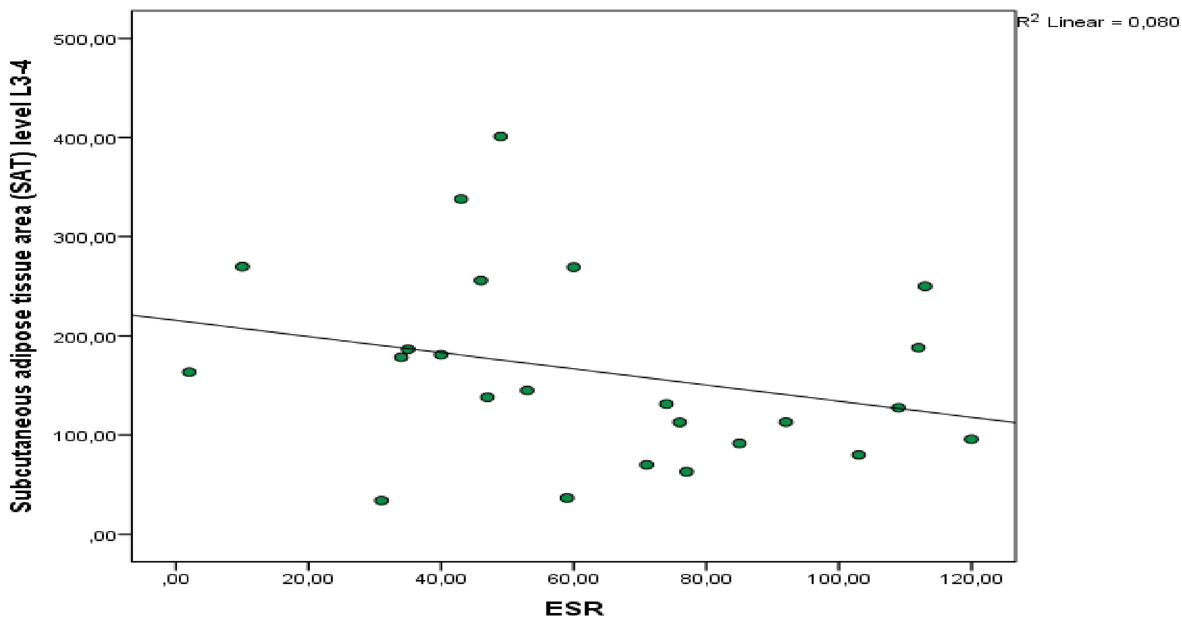

Fig. 69. Dependence between the levels of ESR and the area of subcutaneous adipose tissue at the level of L3-4

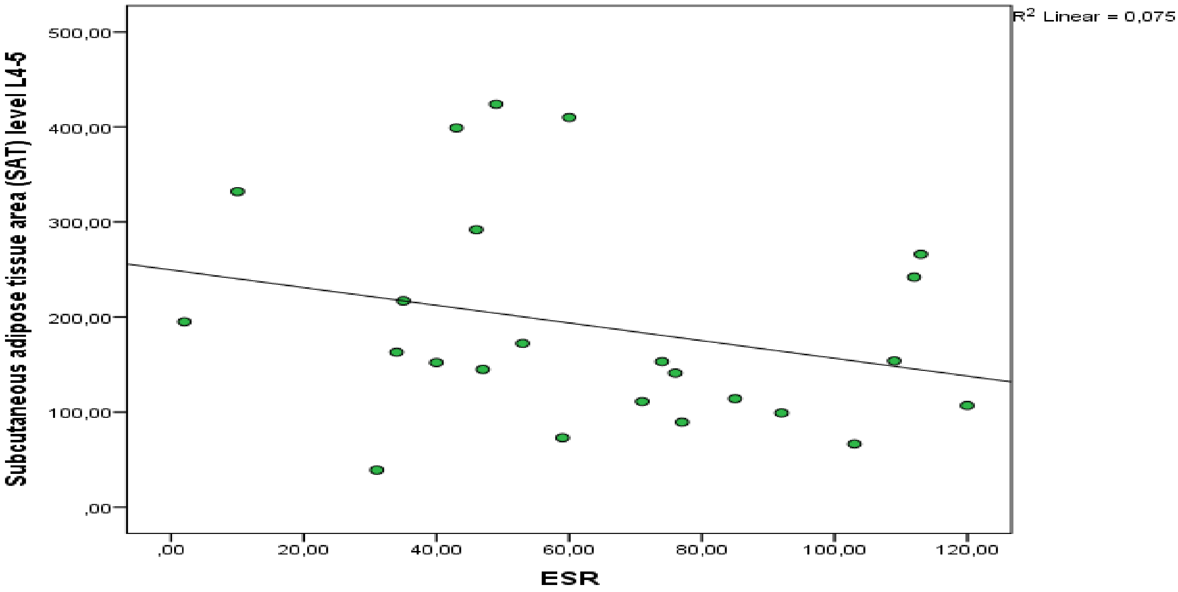

Fig. 70. Dependence between the levels of ESR and the area of subcutaneous adipose tissue at the level of L4-5

From the obtained results, it can be concluded that the serum levels of ESR correlate negatively with bone density and the area of subcutaneous adipose tissue.

A fourth indicator was also investigated, which correlates with the inflammatory process and is related to the adipose tissue evaluation indicators. This is blood sugar. Mean glucose levels in the present sample were 8.89 mmol/L ± 5.49 mmol/L and ranged between 4.40 mmol/L and 33.67 mmol/L. No significant difference was found in glucose levels according to the studied group of patients, as well as according to the presence of sarcopenia.

An inversely proportional moderate relationship was found between serum glucose levels and the volume of subcutaneous fat tissue ($r=-0.305$; $p<0.05$) (Fig. 71).

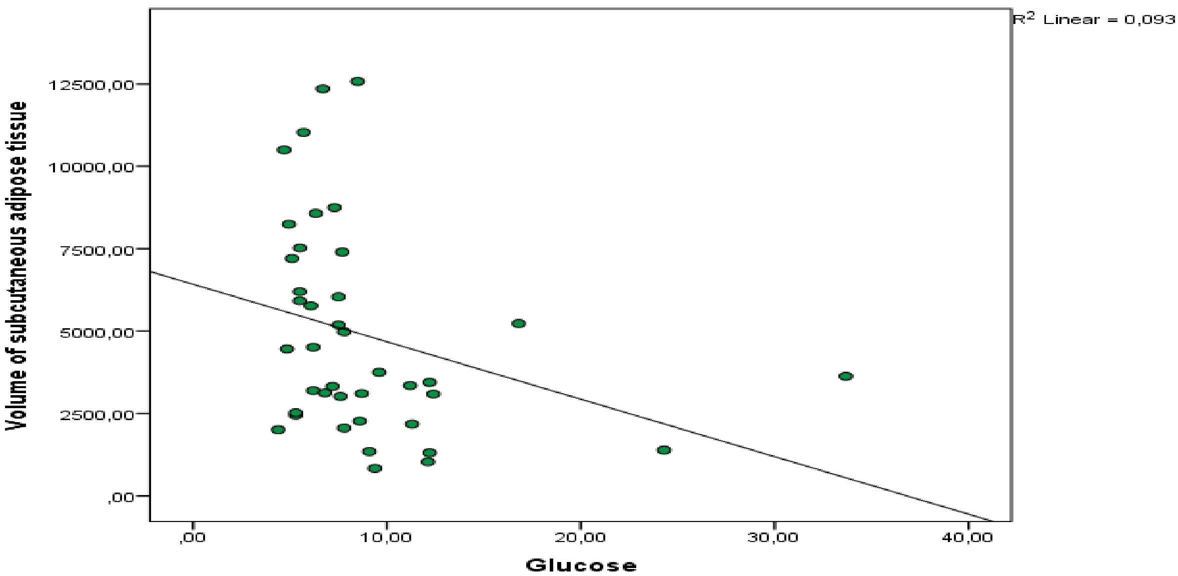

Fig. 71. Dependence between serum glucose levels and the volume of subcutaneous adipose tissue

On the other hand, when examining the relationship between serum glucose levels and the average density of subcutaneous fat tissue, a moderate right-proportional relationship was found (r= 0.369; p<0.05) (Fig. 72).

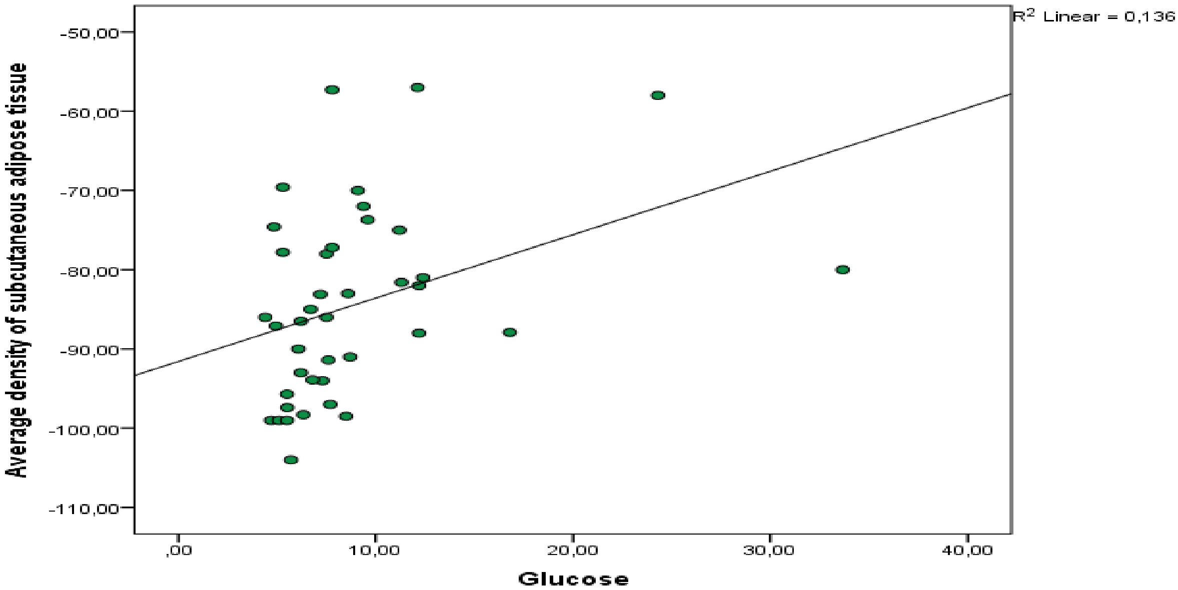

Fig. 72. Relationship between serum glucose levels and average density of subcutaneous adipose tissue

No correlation was found between glucose levels and visceral adipose tissue volume, but a weak to moderate directly proportional relationship was observed with mean visceral adipose tissue density (r= 0.291; p<0.05) (Fig. 73).

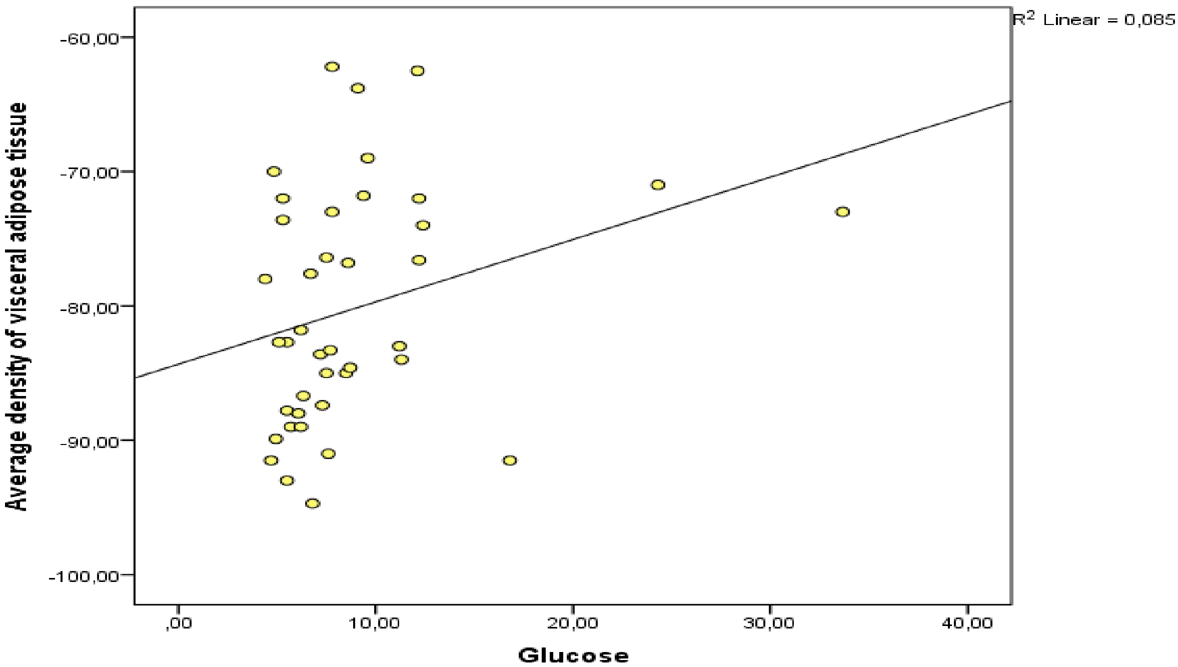

Fig. 73. Relationship between serum glucose levels and mean visceral adipose tissue density

An inversely proportional moderate relationship was found between serum glucose levels and the area of subcutaneous adipose tissue at the L3-4 level (r=-0.365; p<0.05) and at the L4-5 level (r=-0.334; p<0.05) (Fig . 74 and Fig. 75).

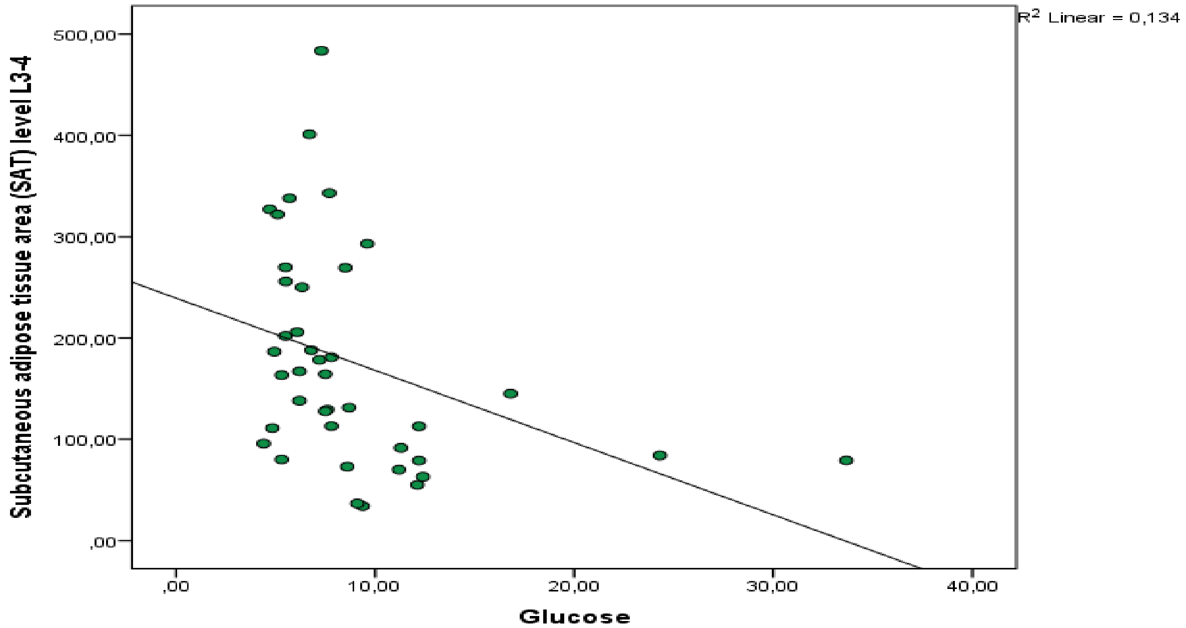

Fig. 74. Relationship between serum glucose levels and the area of subcutaneous adipose tissue at the L3-4 level

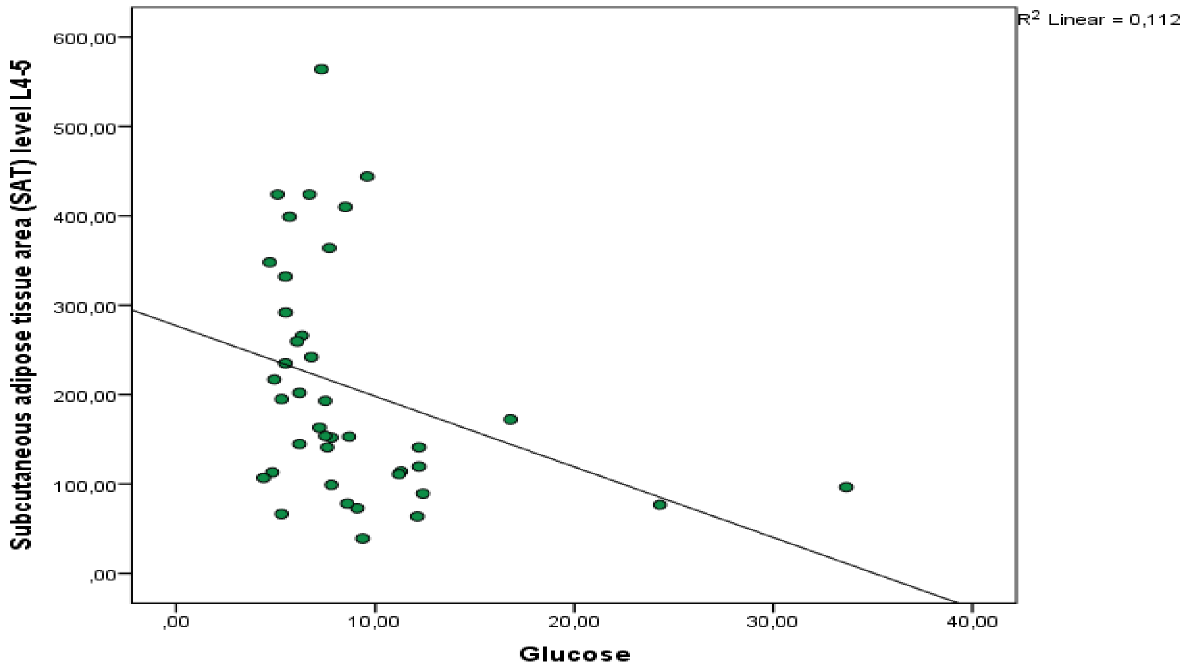

Fig. 75. Relationship between serum glucose levels and the area of subcutaneous adipose tissue at the L4-5 level

No significant relationship was found between serum glucose levels and the area of visceral adipose tissue at the L3-4 level and at the L4-5 level.

V. DISCUSSION

5.1. Examination and analysis of the distribution and density of subcutaneous and visceral adipose tissue

Visceral fat is defined as intra-abdominal adipose tissue associated with the parietal peritoneum or transversalis fascia, excluding the spine and paraspinal muscles; subcutaneous fat is fatty tissue located superficially on the abdominal and back muscles.

CT can be considered the gold standard not only for assessing adipose tissue, but also for measuring many areas of the body [Chowdhury B, et al., 1994; Sjöström L, et al. 1996]. The reported error for determining total fat volume after 28 scans was 0.4%, supporting the high reproducibility of CT.

The amount of visceral adipose tissue increases with age in both sexes, and this increase is present in normal weight (BMI from 18.5 30 kg/m2 to 24.930 kg/m2) as well as in overweight individuals (BMI from 25 30 kg /m2 to 29,930 kg/m2) and obese (BMI > 30 kg/m2), but more in men than in women [Bouchard C, et al. 1993; Enzi G, et al. 1986; Borkan GA, et al. 1983]. On the other hand, the present study did not establish a relationship between the volume of visceral adipose tissue and the age of the patients. Although no significant difference was found, the results of our study also confirmed that the amount of visceral adipose tissue was greater in men than in women (respectively 5265.76 for men and 4033.81 for women).

In a study of 130 subjects (62 men and 68 women with a wide range of ages and weights), Enzi et al. [Enzi G, et al. 1986] found that in young women, lean or obese, the area of subcutaneous abdominal fat predominated over abdominal visceral fat, both measured by CT at the level of the upper renal pole. This adipose topography persists in young and middle-aged women until about age 60, at which point there is a shift to an android-type distribution of adipose tissue. This age-related redistribution of body fat is due to both absolute and relative increases in visceral fat stores, particularly in obese women, which may be associated with increased androgen activity in On the other hand, they showed, menopausal women. Men at any age tend to accumulate fat in the visceral depot, which increases with age and leads to an increase in BMI. In men, a close linear correlation between age and visceral fat volume has been demonstrated, suggesting that visceral fat increases continuously with age [Matsuzawa Y, et al. 1996]. Although this correlation is also present in women, the slope is very slight in the premenopausal state. It became steeper in postmenopausal patients, almost the same as in men [Matsuzawa Y, et al. 1996]. Additionally, Enzi et al. [Enzi G, et al. 1986] found that 7.3% of the women in their study had an android type of body fat topography and 6.5% of the men had a gynoid type of fat distribution.

From the published data [Enzi G, et al.1986] it can be concluded that both subcutaneous and visceral abdominal fat increase with increasing weight in both sexes, but while abdominal subcutaneous fat decreases after the age of 50 in obese men, it increases in women. until the age of 60-70 years, at which point it begins to decrease [Zamboni M, et al.1996]. Correlations of abdominal visceral fat mass assessed by CT or MRI scan with total body fat ranged from 0.4 to 0.8, with higher values obtained when a large range of low and high individuals were present in the population BMI [Sjöström L 1988; Ferland M, et al 1989; Seidell JC, et al. 1988; Desprès J-P, et al. 1991; Sjöström L, et al. 1986]. The results of the present study also showed that visceral and subcutaneous fat volume correlated strongly directly with BMI ($r=0.633$; $p<0.001$ for visceral fat and $r=0.892$; $p<0.001$ for subcutaneous fat, respectively).

Fowler et al. [Fowler PA, et al. 1991] evaluated total and subcutaneous adipose tissue with multislice magnetic resonance imaging in obese and lean women and found that the main difference between them was in the percentage of subcutaneous fat in the abdomen, which was lower than in the thighs in lean, while there were no significant differences between both sites of subcutaneous adipose tissue have been observed in obese individuals. Finally, as previously stated, visceral fat is more sensitive to weight loss than subcutaneous adipose tissue because omental and mesenteric adipocytes, the major components of visceral abdominal fat, have been shown to be more metabolically active and sensitive to lipolysis [Björntorp P 1992].

Lemieux et al. [Lemieux S, et al. 1994] indicate that the gender difference in visceral adipose tissue accumulation is an important factor in explaining gender differences in the cardiovascular risk profile. In addition, adjustment for differences in visceral fat between men and women eliminated most of the gender differences in cardiovascular risk factors. There is evidence to support the idea that the accumulation of abdominal visceral fat is an important correlate of features of the insulin resistance syndrome [Després J-P 1991a; Després J-P 1991b; Després J-P 1993], but this should not be interpreted as supporting the idea of a causal relationship between these variables [Després J-P 1996].

In this study, we evaluated the distribution of body fat in patients with colorectal carcinoma based on diagnostic CT scans, with the aim of investigating the relationship between adipose tissue distribution and gender and age. Computed tomography-based area-based quantification of adipose tissue compartments has been shown to be reliable and reproducible. In the literature, L3/4 and L 4/5 levels are considered comparable to volume-based measurements and are strongly associated with obesity-related mortality such as diabetes or hypertension [Irlbeck T, et al. 2010; Ballentine CJ, et al. 2010]. Women showed higher VAT values compared to men (4107.71 for women and 3479.35 for men, respectively). In addition, younger patients (<61 years) had higher VAT than older patients (4028.44 for patients under 61 years and 3724.44 for patients over 61 years, respectively). This is important because a specific pathogenic role has been attributed to visceral adipose tissue and therefore patients at risk of obesity-related diseases can be identified by quantifying adipose tissue compartments.

Previous studies have modeled adipose tissue using categories, leading to conflicting findings. In a retrospective cohort study of 62 patients with stage I–III colorectal cancer, an area of visceral fat greater than 130 cm 2 was associated with a statistically significant higher risk of all-cause mortality (hazard ratio [HR] = 7.0, 95% CI = 2.0 to 24.6) [Lee CS, et al. 2015]. In another study of 219 patients with stage I–III colorectal cancer, visceral fat in the upper 50th percentile was associated with a statistically significant higher risk of disease recurrence and mortality in patients with stage II disease (HR = 2 .72, 95% CI = 1.21 to 6.10) and a pattern of lower risk of disease recurrence and mortality in patients with stage III disease, but this did not reach statistical significance (HR = 0.50, 95 % CI = 0.23 to 1.06) [Rickles AS, et al. 2013]. Unlike the previous study [Rickles AS et al. 2013], no effect modification by cancer stage was identified in the current study. Prognostic associations of obesity were independent of muscle area, which has previously been reported as a predictor of mortality in cancer patients [Shachar SS, et al. 2016]. In particular, moderate amounts of visceral adiposity among men and moderate amounts of subcutaneous adiposity among women were not associated with mortality; the lowest mortality risks for visceral obesity in men are 130−160 cm2 and for subcutaneous obesity in women are 290−345 cm2.

Obesity is a proven risk factor for the development of many types of cancer and also a negative prognostic factor for many. [Lauby-Secretan B, et al. 2016; Sung H, et al. 2019; Siegel RL, et al. 2019] However, the relationship between obesity and lung cancer outcomes is less clear. Measurement of visceral adipose tissue, according to some authors, is associated with a poor prognosis for lung cancer in patients undergoing chemotherapy. [Nattenmuller J., et al. 2017]

It is well known that the obesity epidemic is a major public health problem because obesity increases the risk of many diseases [Kopelman PG. 2000]. The study showed that regional distribution of adipose tissue was a stronger predictor of health risk than overall obesity [Farkas GJ, & Gater DR. 2018]. Analysis of the distribution of adipose tissue according to gender showed that there was a difference between the volume of subcutaneous adipose tissue in both sexes (5842.53 for men and 9137.46 for women, respectively; p=0.004).

Male VAT is higher than female, while female SAT is higher than male. Sexual dimorphism in the distribution of adipose tissue may be due to different sex hormones [Escobar-Morreale HF, et al. 2014]. Studies show that men have a higher risk of metabolic damage and related diseases than women [Peters SAE, et al. 2019]. VAT is closely related to insulin resistance and type 2 diabetes, cardiovascular disease, hypertension, cancer, sleep apnea, and metabolic syndrome [Tchernof A, & Despres JP. 2013]. Therefore, men may have a higher risk for more visceral fat than women. It has also been reported that reduced SAT volume is associated with metabolic syndrome in women, but increased SAT volume has an adverse effect on metabolic syndrome in men [Matsha TE, et al. 2019]. Low SAT volume in women is also associated with increased mortality in cirrhotic patients [Ebadi M, et al. 2018]. Therefore, it is more beneficial for women to have a high SAT volume and for men to have a low SAT volume. The present findings confirm that men have a higher risk of developing metabolic diseases than women.

5.2. Research and Analysis of Sarcopenia Indicators - HUAC, Psoas Index (PI)

Sarcopenia is a condition characterized by a loss of muscle mass, strength and function, such as development and can be related to the conditions of disturbed homeostasis of the body and with advancing age [Santilli V, et al 2014]. Muscle strength, muscle quantity or quality, and physical activity are important elements of the functional capacity of the living organism, and such musculoskeletal degeneration can interfere with daily activities and demonstrates a predictable correlation in terms of adverse postoperative outcomes and increased incidence of complications (mortality, morbidity in major surgical procedures). We found a similar dependence in our study in relation to the different studied groups. The main leading symptoms, such as loss of weight and muscle mass (or strength), weakness and easy fatigue, are an indicative factor in the history of the development of sarcopenia. It is the detailed history and thorough physical examination that are the basis of the correct and timely diagnosis [Ardeljan D. A. & R. Hurezeanu. 2023]. According to Cleveland Clinic specialists, a questionnaire based on self-reported symptoms called SARC-F (S — Strength.; A — Assistance with walking.; R — Rising from a chair.; C — Climbing stairs.; R — Rising from a chair.; C — Climbing stairs.) is widely used. F — Falls Each factor is scored between 0 and 2. The highest maximum SARC-F score is 10. Scores above 4 require further investigation). The factors defined in the world literature are also confirmed by our research in different groups. Age is the dominant factor, but other established possible risk factors for the development of sarcopenia (including physical inactivity) are: obesity; chronic diseases such as chronic obstructive pulmonary disease (COPD); kidney disease; diabetes; They are of different localization; HIV; rheumatoid arthritis; insulin resistance; decrease in the levels of various hormones; malnutrition or insufficient protein intake; disturbed metabolism; neurological diseases [Santilli V, et al. 2014]

Research and analysis of indicators related to sarcopenia can be crucial for the prevention and treatment of this problem. The two measures noted, HUAC (average angular muscle contour) and Psoas Index (PI - Psoas muscle index), are important tools for measuring and evaluating muscle mass. The literature discussion is organized around the following aspects: In conditions such as malignancy, rheumatoid arthritis, and aging, Psoas Index mass is lost, while HUAC may be preserved or even increased. The loss of muscle mass can be associated with an increased BMI, so that despite a normal weight, marked weakness is found, or so-called sarcopenic obesity [Cruz-Jentoft AJ, et al. 2019]. The established correlation between inactivity and loss of muscle mass and strength suggests that physical activity should be a major factor for prevention, but also for early diagnosis and treatment of sarcopenia. Our study confirms the strong correlation of signs and an increase in the risk of sarcopenia, which increases with a long duration of symptoms in patients with colorectal cancer, lung cancer and pancreatitis. In a study conducted by the Japanese Society of Hepatology among 504 patients, low values of the HUAC, PI, SD indicators were found in men (on average 3.30 cm2), while in women the measured values were higher (above and 3.74 cm2 and more). Loss of muscle mass increased with age, and segmentation of patient values showed a significantly higher prevalence of skeletal muscle loss in men and in patients with liver cirrhosis than in those without liver cirrhosis [Ohara M., et al. , 2020]. In our study, when looking in detail at the relationship between gender and the values of measured adipose tissue area and HUAC, it was found that in the colorectal carcinoma group and the pancreatitis group, in men, with advancing age, the measured subcutaneous fat area decreased ($p=0.000$) , and respectively in women it increases ($p=0.000$). This worsens the prognosis for life expectancy and quality of life in days of poor health and long-term disability, in the presence of accompanying diseases, impaired nutrition and progressive muscle weakness.

The recommendations made by the Japanese Society for suspected or proven sarcopenia with clinical frailty is to ensure that the sarcopenic patient can be copied with proper and sufficient nutrition as early as possible [Huang DD, et al. 2015].

A multicenter study among 1,787 individuals found that early measurement of parameters in patients, regardless of the reason for hospitalization and correct interpretation of the data, had a beneficial effect on life expectancy. 5th percentile index values were defined, and for men, L3-PMI values decreased with age (5.41 cm2/m2 for 20-29 years, 4.71 cm2/m2 for 30-39 years, 4, 65 cm2/m2 for 40-49 years, 4.10 cm2/m2 for 50-59 years and 3.68 cm2/m2 for over 60 years). The reference values for women are lower. The recommendations made are to be introduced into the routine practice of specialists, the measurement of the relevant indicators (SAT, VAT, HUAC, conducting an imaging study and consultation with a specialist imaging diagnostician), which will prevent or postpone the onset of this condition as much as possible, affecting improve QOL and reduce the burden of long-term care demand [Kong M, et al. 2022]. The multi-centre study conducted among 1453 patients from the Department of Surgery, Royal Marsden Hospital, Department of Surgery and Cancer, Imperial College, Chelsea and Westminster and the Royal Marsden Campus, Paddington, Colorectal Surgical Unit, Chelsea and Westminster Hospital, Chelsea and HCA Healthcare in London , UK, found that of applied imaging methods to measure cross-sectional area and parameters used to define sarcopenia. significant variability was observed in defined skeletal muscle values depending on the current condition (accompanying disease or symptom complex). The measured values of patients in the acute phase are lower, compared to subsequent measurements, after therapy. An increased risk of postoperative complications favoring the appearance of sarcopenia is found. Scientists are finding that sarcopenia is a modifiable risk factor because skeletal muscle mass can be modified. [Clark, S.T., et al. 2020].

Sarcopenia is a concomitant morbidity among patients with CHF (Congestive Heart Failure), which adversely affects the prognosis of the disease itself. The results of the SICA-HF study showed that the incidence of sarcopenia in patients with CHF was almost 20% higher than in healthy subjects. Peripheral skeletal muscle loss occurs early in most HF patients (measured low HUAC and Psoas Index values, well below normal), regardless of reduced or preserved ejection fraction, which is closely related to reduced physical activity [Yin J., et al. 2019].

A study among the Turkish population in the period June 2010 - April 2018 aimed to determine the values of skeletal muscle indices HUAC, total skeletal muscle index (SMI) and Psoas Index (PMI/PI) at the level of L3 vertebrae by computed tomography to assess low muscle mass among 601 patients, of whom 326 were men. Limit values of indicators for the 5th percentile are defined as 5.40 cm2/m2 (PMI)/ 41.42 cm2/m2 (SMI), and for women 3.56 cm2/m2(PMI)/30.70 cm2/m2(SMI). The results found are comparable to other populations [Bahat G, et al. 2021]. Another study among 157 patients diagnosed with multiple myeloma (MM) in Merdin, Turkey, found mean high 5th percentile values for HUAC and PMI (41.44±8.11 and 36.98±7.13), with no clear correlation between HUAC, PMI and Body Mass Index (BMI) [Koyuncu Mahmut, et al. 2021].

The establishment of muscle weakness in the course of diagnostic clarification and in the presence of sarcopenia has an impact on mortality in these patients, mainly with pronounced sarcopenia. It is defined that the retrospective score of the Clinical Frailty Scale can be used to predict the FP in good health, relatively in the early stages when the first symptoms are established. The defined scale has been confirmed by other studies and is widely used in diagnosis [Fatani H., et al. 2023; Xu Jing-Yong, et al. 2020].

In our research, established methods were used and a number of indicators HUAC, PMI/PI, SAT L3-4/L4-5, VAT L3/4, VAT L4/5, SD, etc. were measured, resulting in the diagnosis and interpretation of leading stance on good clinical behavior. Significant correlations were found with the severity and duration of symptoms, hospital stay and outcome of the disease, which confirms that imaging studies are important for early diagnosis (deteriorated condition on admission and HUAC (p=0.034), with a significant relationship established for the outcome from disease - df=8, Cramer's V=0.959, r=0.341). High values for the 5th percentile were measured in men and women in the studied groups, which worsens the prognosis for LFS and quality of life in days of long-term disability.

HUAC and Psoas Index measurement methods, as well as their accuracy and reliability, are early prognostic and diagnostic markers of the patient's clinical behavior and LFS [Mei, K.L., et al. 2016].

5.3. Assessment of bone density with computed tomography using phantoms

Osteoporosis is a disease that is associated with low bone mineral density (BMD). Patients with osteoporosis are at increased risk of fractures, which in turn lead to prolonged hospital stays, bed rest, rehabilitation and high mortality, thereby increasing the economic costs of treatment [Sànchez-Riera et al 2014]

Determination of bone mineral density appears to be an important and independent predictor of future fracture risk and all-cause mortality [Buckens CF, et al 2015; Cosman F, et al 2014].Ранното откриване и своевременното лечение наостеопорозата чрез на измервания на BMD може да допринесе за превенция на остеопоротичните фрактури [Cosman F, et al 2014]

According to the World Health Organization (WHO), dual-energy X-ray absorptiometry (DXA) is the preferred method for assessing bone mineral density (BMD) and examining patients with osteoporosis [Kanis JA, 1994]. DXA is the gold standard and frequently applied X-ray method, due to its wide availability, lower cost of examination and low dose of ionizing radiation.

However, in adult patients, the use of the projection DXA technique, which measures areal BMD (aBMD) in g/cm2, has been found to be sometimes in error. There is a relationship between size and area of measured bone density, the other reason being artifacts that cause inaccuracies (eg, superimposed soft tissues, aortic calcifications, vertebral fractures and degenerative changes of the spine, spondylochondrosis and osteochondrosis) and whole bone measurements, as as DXA measures the entire vertebra, including the neural arch, thus including the cortical bone [Watts NB, 2004], while the inner trabecular bone appears to be more metabolically active and therefore more affected by changes in bone mineral density [Engelke K, et al 2008].

Quantitative computed tomography (QCT) is not affected by the above artifacts and at the same time allows differentiation of cortical from trabecular bone [6]. However, QCT is associated with a higher dose of ionizing radiation and usually requires a phantom for calibration during scanning, which eliminates the option of routine BMD measurements at times of CT examination for any indication. Recent studies have suggested the use of CT scans for the use of BMD assessment, as CT shows a much higher sensitivity and specificity of 62–93% and 79–97%, respectively, compared to that of DXA [Buckens CF, et al 2015; Pickhardt PJ, et al 2013; Rome EAPM, et al 2012; Engelke K, et al 2015].

Quantitative CT (QCT) allows volumetric BMD measurements to be performed, usually applied to the lumbar spine and calibrated against a reference phantom with known concentrations of calcium hydroxyapatite Ca5(PO4)3(OH) (CaHA). This study outperforms the DXA-based measurement of bone mineral density BMD [Yu, W. et al. 1995] and is also a more sophisticated method of fracture risk assessment such as analysis of individual bone components [Kopperdahl, D. L. et al. 2014; Dall'Ara, E., et al. 2012; Oei, L., et al. 2016].

To reduce the dose of ionizing radiation, modern researchers are focusing on how to routinely use multidetector computed tomography (MDCT) obtained for various reasons, e.g. for morphological imaging, staging of oncological disease, screening for osteoporosis or monitoring the dynamics of a given disease during therapy. [Link, T.M. 2012]. For example, MDCT-derived BMD-equivalent values have been used to predict incident osteoporotic vertebral fractures [Baum, T. et al. 2012], to assess fracture risk in patients with inflammatory bowel disease and prostate cancer [Fidler, J. L. et al. 2016; Schwaiger, B.J. et al. 2017]. There are limitations to all CT-based measurements of BMD, as they can be affected by scan parameters such as varying tube voltages, use of intravenous contrast material, fat content in the vertebral bone marrow, and beam hardening or scatter artifacts from the presence of metal osteosynthesis [Engelke, K. et al. 2015; Garner, H.W., et al. 2017; Goodsitt, M. et al. 1987; Pompe, E. et al. 2015].

Whether used in daily routine clinical practice or specifically for osteoporosis research, BMD phantoms are the first choice for determining bone density or performing quality assurance on CT and DXA.

All BMD phantoms were made with Ca-hydroxy apatite, the material of greatest interest in bone mineral densitometry. Phantoms are calibrated, analyzed and tested to the highest BMD standards. They are designed according to clinical needs.

International standard for spine mineral densitometry by DXA and QCT.

Mandatory for multicenter studies or single-site testing are three vertebrae with different bone mineral content.

The European Spinal Phantom (ESP) with its anthropomorphic design is the ideal tool for the quantitative measurement of bone mineral density of the spine in DXA and QCT.

The ESP resembles the lumbar region of a small adult and has been used as the standard for quality control in QCT and DXA [Kalender WA, et al 1995] accuracy and repeatability and for quantification of spine BMD for more than two decades. Its narrow anthropomorphic design with three internal inserts at the lumbar vertebrae allows standard patient protocols to be used in both DXA and QCT.

The main body of the phantom consists of a water-equivalent resin. The three lumbar spine inserts contained different, well-defined values of Ca5[OH|(PO4)3] (Ca HA) of 50, 100 and 200 mg/cm3 of HA mimicking (patho) the physiological range of BMD in all age groups. Measured on

DXA, these vertebral inserts represent the BMD zone (aBMD) of 0.5, 1.0, and 1.5 g/cm2 HA, respectively.

This phantom allows verification of the reproducibility and accuracy of the following quantitative parameters:

- bone mineral density area (BMD area) in g/cm² for DXA
- trabecular and cortical volume bone mineral density (volume BMD) in g/cm³ for QCT
- cortical thickness in mm for QCT
- positioning accuracy in QCT

https://www.qrm.de/en/products/european-spine-phantom#c11691

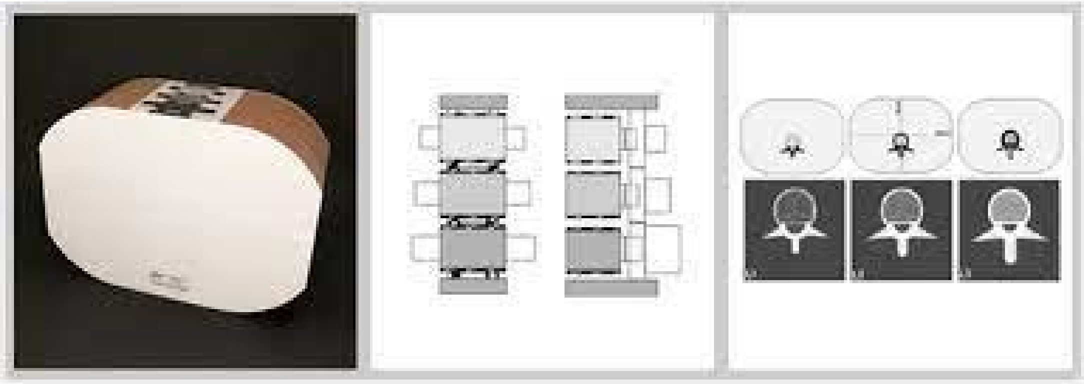

Fig. 76. Anthropometric European spinal phantom ESP

There are other types of phantoms that are used in daily clinical practice - forearm phantom, femur phantom. The only drawback is the high cost of phantoms and the high cost of Ca5[OH|(PO4)3].

5.4. Investigation and assessment of the relationship between bone density and subcutaneous and visceral adipose tissue

The search for relationships between SAT status, VAT and bone density is determined by the fact that the number of elderly people (over 65 years) is increasing worldwide. In 2017, the number of elderly people represented 13% of the world's population and is expected to reach 2.1 billion people by 2050 (database, 2017). Most chronic conditions worsen with aging, which itself is associated with profound changes in body composition, ie. increase and redistribution of fat mass and loss of muscle and bone mass [Batsis JA, & Villareal DT, 2018]. Among the most common conditions is obesity (defined as a BMI of 30 kg/m2), a complex and multifactorial disease that has become a worldwide pandemic [Bray GA, et al. 2017]. In several countries, the prevalence of obesity reaches 30-40% of the population and its incidence is expected to increase significantly in the coming decades. It is therefore not surprising that obesity is associated with over 200 medical complications and an increased risk of morbidity and mortality, representing the fifth leading cause of death worldwide [Bluher M, 2019]. Decreased muscle mass and strength (sarcopenic obesity) is closely related to bone density, and in a state of impaired homeostatic reserve and stress tolerance, as determined by measurements of SAT, VAT, HUAC, has been shown to increase the risk of adverse health consequences [Fielding RA, et al. 2011]. Sarcopenic obesity is strongly associated not only with cardiometabolic dysfunctions but also with physical disability [Batsis JA, & Villareal DT 2018].

The main goal of a number of studies is to analyze different measurements of adipose tissue density to establish relationships with the general condition. A large-scale national study in the United States, using a multiple linear regression model for estimation, found an association between visceral adipose tissue, subcutaneous adipose tissue, and BMI. A total of 10,455 participants between the ages of 20 and 59 were studied. Various weighted multiple linear regression models showed a negative correlation between lumbar BMD and visceral mass index (VMI) and subcutaneous mass index (SMI). However, the relationship between VMI and lumbar BMD showed a U-shaped pattern using the smooth curve, and the inflection point of 0.304 kg/m2 was determined using a two-stage linear regression model (the point at which pathologic inversion occurs). This leads to the development of various pathological conditions (osteoporosis, severe pain syndrome, etc.). Over 53.4 million people of working age in the United States suffer from changes in bone density (osteoporosis, osteopenia, muscular dystrophy, sarcopenia), and the incidence of these conditions steadily increases as the population ages. This factor aggravates health care costs, which in the long term are expected to undergo a staggering escalation of 100-200% by 2040, due to prolonged hospitalizations [Lin, Y., et al. 2023].

Older people show more systemic lipolysis and oxidation of dietary fat but less lipid storage in SAT according to a study using mCi [l-14C] to monitor dietary fatty acids [Koutsari C, et al. 2009]. The inability of SAT to store excess energy leads to deposition of lipids in cisternae and other ectopic depots (eg, skeletal muscle, liver, pancreas, heart). This phenomenon is further exacerbated by the chronic positive energy balance characteristic of obesity [Zamboni M, et al. 2014]. An excessive caloric load follows adipose tissue expansion, which may occur through adipocyte hypertrophy.

In the conducted research, we found a moderate relationship between the outcome of the disease and the hospital stay in the different groups (p=0.061), the HUAC indicators measured (p=0.034), with a significant relationship established (df=8, Cramer's V=0.959, r= 0.341). The obtained results prove that the severity of the disease and the baseline state have a leading role in terms of the length of hospital stay and the prognosis of recovery and good health.

The presence of General Musculoskeletal Pain is defined as an indicator of group h of the Relevant Health Policy Area - having a significant degree of severity. The defined indicator is placed in the 37th position, in terms of significance and influence on the body for the development of pathological conditions. When it is part of a very complex symptomatology, musculoskeletal pain is leading to the severity of the condition [Arnaudov Y. 2014].

The World Health Organization defines individuals at risk as having bone mineral density (BM) at least 2.5 standard deviations below the mean for healthy young adults. BM serves as an approximate measure of the amount of bone tissue in the skeletal frame, and its decline predisposes to the development of osteoporosis and/or sarcopenia. Identifying the risk factors that contribute to the reduction of BM is of paramount importance in preserving the health of the individual (bone condition) and preventing the subsequent complications [Shuler, F. D., et al. 2012]. We definitely found malnutrition in all groups, especially in patients with newly diagnosed diseases, more often in patients with initial evidence of an inflammatory episode within the last year, as well as in those with higher overweight. Although there is an obvious certain phenotype of disordered eating habits, timely measures are not taken in a diagnostic and treatment plan to control the causes leading to eating disorders. In all patients, deviations in laboratory indicators (glucose, albumin, hemoglobin) were found. Altered nutrition, the presence of insulin resistance increase the risk of developing sarcopenia (measured low values with more than 2.5 points of HUAC, SAT, VAT than in controls), cancer of different localization (bladder, breast, colon, cervix , pancreas, prostate), and the risk is higher in men 1.06%.

Copying the disturbed processes, through proper nutrition and carrying out dietary nutrition in the recovery period are important, both for the outcome of the acute illness, and for improving the quality of life and reducing the days of temporary or permanent incapacity. Diet is a factor that is also important for the prevention of subsequent complications, since the lack of nutrients is a predictor of a number of other diseases.

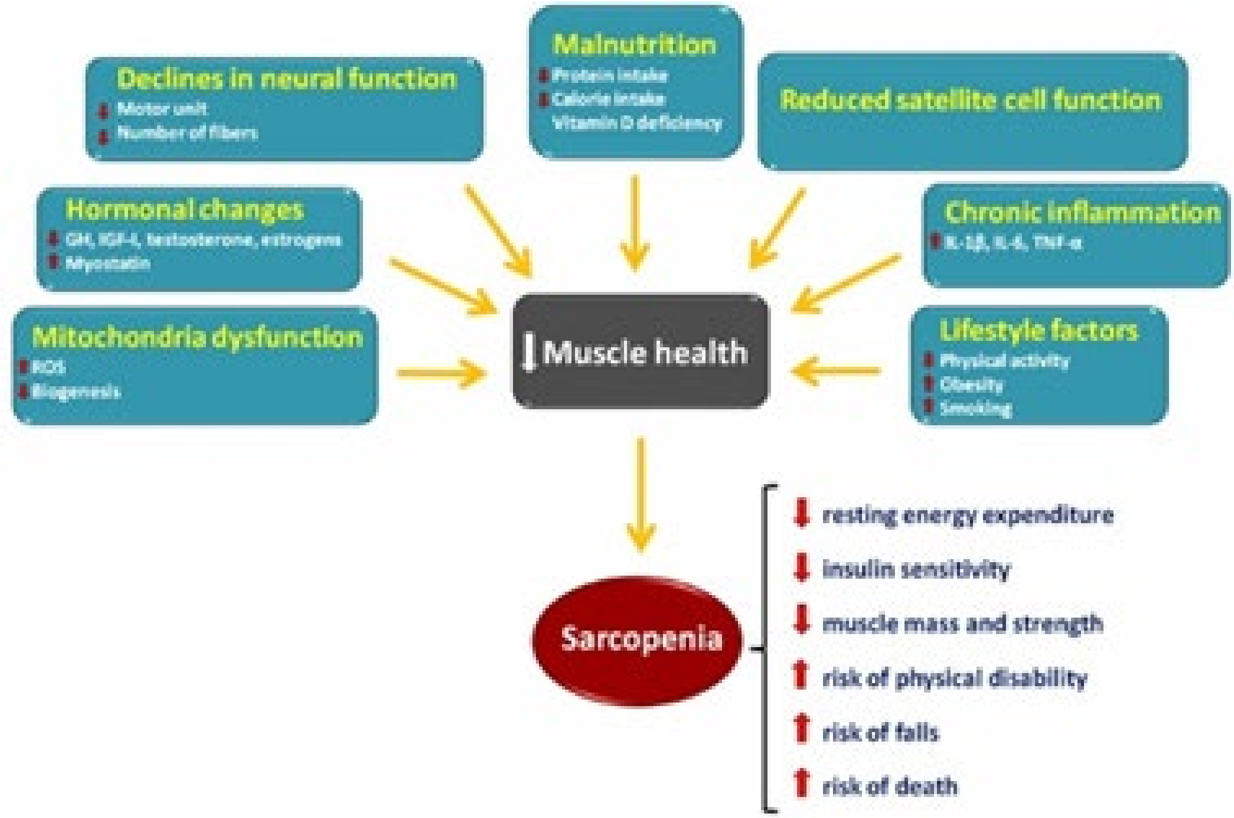

Fig. 77. Pathophysiology of sarcopenia [M. Mosaferi Ziaaldini, et al. 2017]

Fig. 78. Pathogenesis and interventional impact on sarcopenia (J.Jang, et al. 2023)

The results of conducted studies support the claim that the relationship between adipose tissue and BM exhibits variations dependent on baseline weight (BMI). Various changes in the body, hormones and inflammatory markers (inflammatory conditions) that can be excreted from adipose tissue affect the main cellular processes (increased insulin resistance, increased active metabolic profile). Measured higher VAT and SAT determine the presence of various inflammatory conditions. Therefore, when investigating the impact of adipose tissue on human health, it becomes imperative to consider the specific type of adipose tissue and to measure values of bone density and subcutaneous and visceral adipose tissue [Gilsanz V, et al. 2009].

In a study of adolescents with postpubertal obesity, measures of visceral adipose tissue and BMD were measured. No significant differences were found between groups (men and women) for subcutaneous fat (kg), insulin (g/ml), BMI (kg/m2), total BMD (g/cm2), spine BMD (g/cm2). Males presented higher scores for visceral fat tissue, glucose, weight, height, total fat tissue compared to females. Descriptive data were checked for statistical errors and biases with the non-parametric Kolmogorov-Smirnov test, statistical significance was set at $\alpha < 5\%$ [Campos R. M. S., et al. 2012].

In our study, the results in all groups were verified by the Kolmogorov-Smirnov test, as well as by additional tests for the reliability of the results (Shapiro-Wilk, Cronbach's Alpha, Cramer), which ensure comparability and comparability of the results with the global base data. The applied verification models prove the reliability of the results and the uniform distribution of the samples.

Crivelli M. and team investigated the relationship of visceral and subcutaneous adipose tissue with bone mineral density (BMD), defining the values of femoral bone density indicators, in pre- and postmenopausal women and the presence of severe obesity. In postmenopausal women, total subcutaneous fat was inversely associated with BMD at total femur (β = -0.009; 95% confidence interval [CI] -0.017, -0.002) and with strength index (β = -0.03; 95 %, CI -0.04; -0.01). In premenopausal women, visceral adipose tissue is inversely related to subcutaneous adipose tissue [Crivelli M., et al. 2021].

In the period 2011-2018, Longti Li and colleagues conducted a study among 11,227 people from the American population, establishing a relationship between body mass ratio, visceral fat mass and bone mineral density. Considers the importance of harmful habits (smoking, alcohol, drug abuse). It found a consistent positive correlation between total muscle mass and BMD in all age subgroups. A negative correlation was observed between visceral fat mass and BMD, with a positive correlation in diabetic patients [Longti Li, et al. 2023]. Our results show a negative association between subcutaneous adipose tissue and BMD. The measured values of the parameters of the subcutaneous adipose tissue for the control group were significant for the risk of developing insulin resistance and increased the risk of developing sarcopenia in a large number of cases of indicators above 25 Percentile for the group of men (n=29). In the same group, a detailed examination of the relationship between gender and the values of the measured subcutaneous fat area (SAT) level L3-4 [cm2] found that in men with advancing age the measured subcutaneous fat area (SAT) level L3 -4 [cm2] decreases (p=0.000), and respectively in women it increases (p=0.000).

Lean body mass is a function of total body weight, excluding adipose tissue or fat. One of the most important components of lean mass is skeletal muscle, which defines movement and stability. Despite being a passive structural element, skeletal muscle functions as an endocrine organ that releases a wide range of muscle factors (myokines, insulin-like growth factor-1, fibroblast growth factor-2, neurotrophic factor, etc.) that play a role in regulating other cells and processes in the body [Banfi G, et al. 2020]. Xiao's study found a strong relationship between bone density and subcutaneous fat, and muscle mass was the leading predictor of BMD in both sexes [Xiao Z, et al. 2020].

4.5. Investigating and assessing the relationship between CT indices of subcutaneous and visceral adipose tissue, bone density and sarcopenia

A study by Carmelo Messina and colleagues focused on the ability to assess visceral and subcutaneous adipose tissue. Measurements of VAT according to SAT showed a high correlation with the change in bone density, with sample confidence p=0.93. It defines the reference values for the National Health and Nutrition Examination Survey (NHSN), which become a marker for the categories of obesity based on the muscle mass of the patients [Messina C., et al. 2020].

Observation of a group of patients with endocrine diseases found early predictors in laboratory tests (mean levels of serum albumin and protein 3.2 g/dL and 6.6 g/dL) and low measured SAT indicators (4.8) compared to controls (5.7) (-18% deficit, p=0.06), compared to healthy controls (67.3) (-17% deficit, p=0.20). Visceral adipose tissue estimates made by perinephric index were also lower [Nagaraju S., R. et al. 2020]. The same study assessed the risk of Sarcopenia, by measuring L2/L3 and L4/L5, assessing the total muscle area and subcutaneous fat area, the intervertebral space by CT. Sarcopenia was observed in patients with type 1 diabetes, regardless of whether it was the main disease or accompanying the main one, regardless of the duration of the disease compared to controls. Sarcopenia was markedly more severe in long-term patients with more than 20 years of disease duration (-16% and -12%, versus -34%). A deficit of subcutaneous adipose tissue was found compared to controls (-24%, -31%, and -9%, p=0.29), more pronounced in men. Visceral adipose tissue deficiency was found in 56% of the examined persons. Nagaraju and his team found that progressive muscle weakness leads to a progressive reduction of SAT, VAT values by more than 5 points from the reference values for age [Nagaraju S., R. et al. 2020].

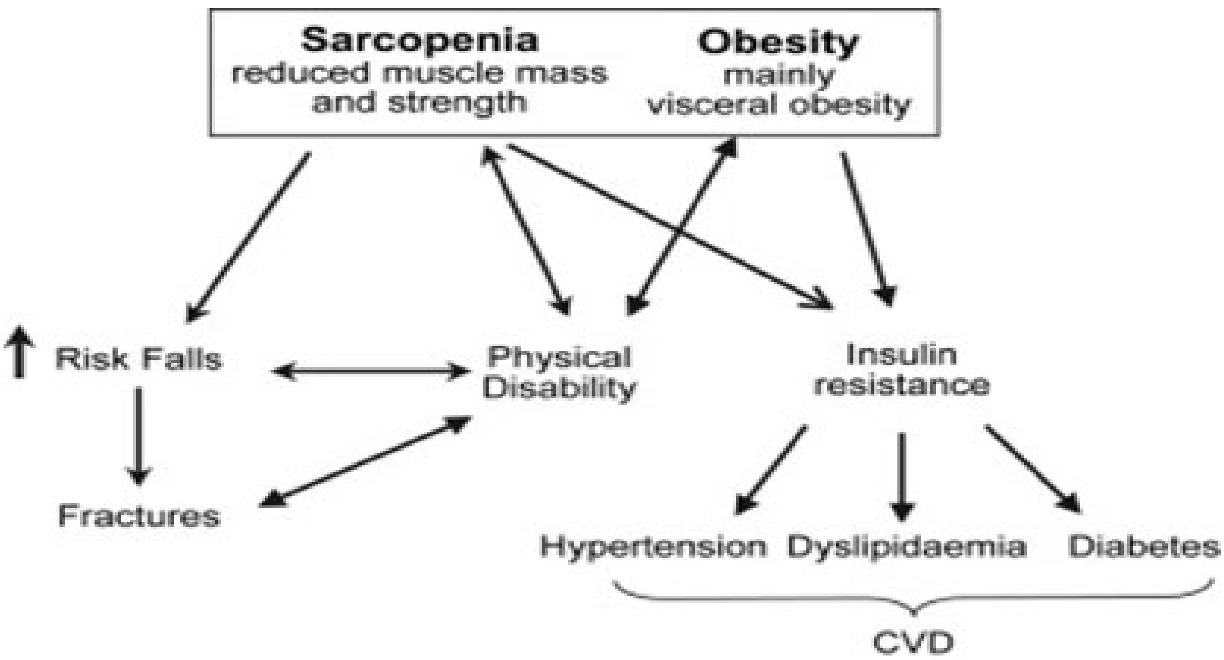

Fig. 79. Consequences of obesity (adapted from Zamboni et al. 2008)

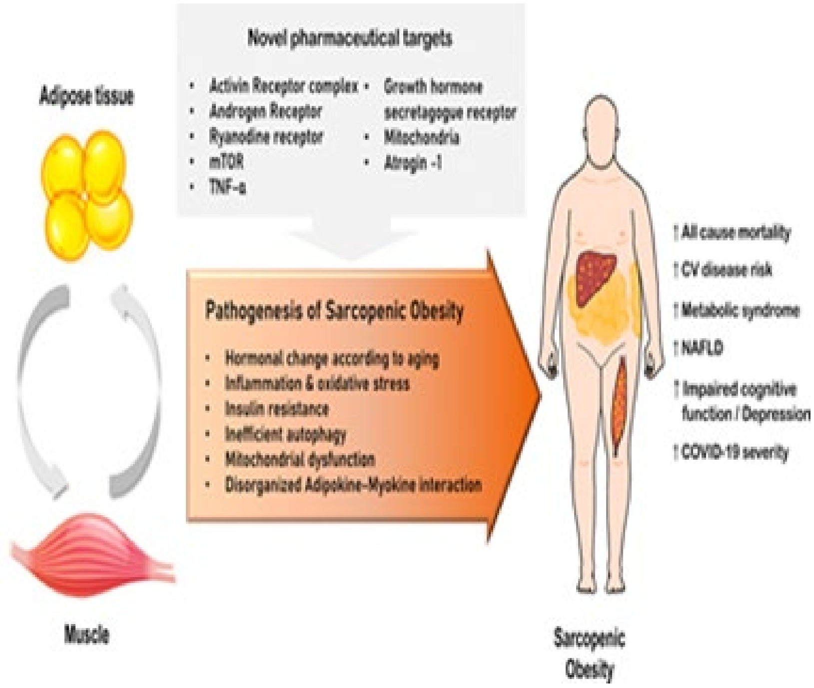

Fig. 80. Obesity as a Factor in Sarcopenia (Adapted from Min Jeong Park, Kyung Mook Choi, 2023)

In the analysis of the data from our own study, we found a dependence among men, when measuring the subcutaneous fat tissue (p=0.000). A detailed examination of the relationship between gender and measured subcutaneous fat area (SAT) at L3-4 level [cm^2] found that in men with increasing age, measured subcutaneous fat area (SAT) at L3-4 level [cm^2] decreases (p=0.000), and respectively in women it increases (p=0.000).

In the data obtained among patients with endocrine diseases, we found that the risk of developing sarcopenia (1.07%) increases in patients with diabetes mellitus type 2 (with n=7 in a confidence interval of 95%), and the risk increases twofold in the presence of insulin resistance (n=16), which increases the risk of liver damage and heart disease. This is an indicator of correlation and comparability of our results with the scientific database.

An inverse relationship was established between the risk of developing or having sarcopenia and laboratory data on serum albumin (the risk increases with low albumin values, with a change of more than 2 units from the reference values and the presence of disease) [Nagaraju S., R. et al. 2020].

There is evidence that visceral adipose tissue (VAT) is a prognostic indicator of sarcopenia risk because visceral fat cells are metabolically active and the presence of other clinical factors such as fever, infectious disease, surgical disease, pathological process in bones and metabolic organs) reflect visceral adipose tissue measurements because it is metabolically active from subcutaneous adipose tissue. Visceral fat cells release proteins that contribute to inflammation, atherosclerosis, dyslipidemia, and hypertension. Changes in measured values of more than/or less than 2 to 4 points of visceral adipose tissue increases the risk of all-cause mortality in men and is considered a pathogenic fat depot.

A study by Bulgarian scientists Zh. Boneva and M. Boyanov defines a method of comparing measurements in a control group according to weight with other groups (higher/lower weight). As a norm, they take VAT (cm2)=e(5.757−56.131/age in years); p=0.033, F=7.06, R2=0.502. For the overweight group: VAT (cm2)=54.425+2.429× age in years (p=0.016, F=6.31, R2=0.136). Following the regression analysis, they define the norm for SAT in cm2=267.109−2.295×age in years (p=0.040, F=6.33, R2=0.475) for the study. In the age groups for men 40-49 years. and 50-59 years, the risk of sarcopenia increases 1 x with an increase in the measured indicators of VAT (325.0 and 292.0) and SAT (119.8 and 194.0), while in women they do not establish a significant relationship with age, due to the metabolic and hormonal changes occurring in the various age groups. OR of developing sarcopenia for men is 0.299, and for women over 50 is 0.524 [Boneva-Asiova Z., & M. Boyanov. 2011].

In the conducted study, we found significant relationships between - Volume VAT and HUAC in the colorectal carcinoma group (p=0.246), with a significant relationship established (df=399, Cramer's V=0.975, r=0.246). The OR for sarcopenia was 0.87%.

A study among cancer patients determined adipose tissue composition as a prognostic tool in an African population. The measured low values of bone density in oncological patients are the reason for the development of osteoporosis and sarcopenia. In premenopausal women, an increase in WMP values was found compared to a group of age-matched men, a comparison that was reversed in postmenopausal patients [Bates D., & P. Pickhardt. 2022].

In patients with a BMI of 25.1, there is evidence of initial muscle tropism and sarcopenia, which can be corrected with early diagnosis with adequate nutrition. With a lower BMI, sarcopenia was found, and the risk increased with increasing age (by 0.36 up to 40 years, 40-49 years by 0.45, over 50 years by 0.51%). Sarcopenia causes impaired muscle function and decreased bone density regardless of age, leading to osteosarcopenia in the long term.

In patients with type 1 diabetes, lower muscle mass (SAT and VAT, p=0.06) was measured compared to controls in their calculated BMI and BMT indices (p=0.20, at a 17% deficit), with a small difference in BMT [Nagaraju S., et al. 2020].

5.6. Investigation of the influence of the inflammatory process on indicators of subcutaneous and visceral adipose tissue, bone density and sarcopenia

Sarcopenia and obesity are considered multifactorial syndromes, sharing various overlapping causes and feedback mechanisms, continuously influencing each other. Various studies have presented views on the pathogenic relationship between sarcopenia and obesity, without a clear answer as to the leading importance of one of the two factors. A leading role of inflammation and insulin resistance for sarcopenia and obesity is inferred, but the origin of local inflammation and insulin resistance and how they cause systemic inflammation, systemic insulin resistance, and changes in body composition remain unclear. [Li C., et al. 2022].

The same authors investigated the systemic physiological conditions associated with inflammation: excessive oxidative stress and the production of reactive oxygen species having effects on adipose tissue homeostasis and fibrosis. They found that the overproduction of ROS in myoblasts caused the accumulation of S100B enzyme protein molecules (predictor sarcopenic proteins), which promoted the transition of myoblasts to adipocytes, and myoblasts from sarcopenic subjects showed properties of (re)adipocytes. in turn, S100B stimulates NF-κB activity with consequent upregulation of YY1 and YY1-dependent inhibition of microRNA-133, a promyogenic and anti-adipogenic microRNA that induces chronic inflammation in existing fat depots and other tissues, contributing to the pathophysiology of adipose tissue dysfunction. Dysfunction in fat metabolism and gradual impairment of adipogenesis, which contributes to insulin resistance triggering metabolic diseases, activates proinflammatory cytokines such as interleukin (IL)-1β inhibit adipogenesis, or the ability of pre-adipocytes to mature into functional lipid-enriched adipocytes. In a chronic inflammatory microenvironment, preadipocytes transdifferentiate into macrophage-like cells with increased expression of proinflammatory cytokines and decreased adipogenic capacity in response to inflammatory stimuli. This ultimately contributes to a vicious cycle of adipose tissue inflammation, lipolysis and fibrosis. [Li C., et al. 2022].

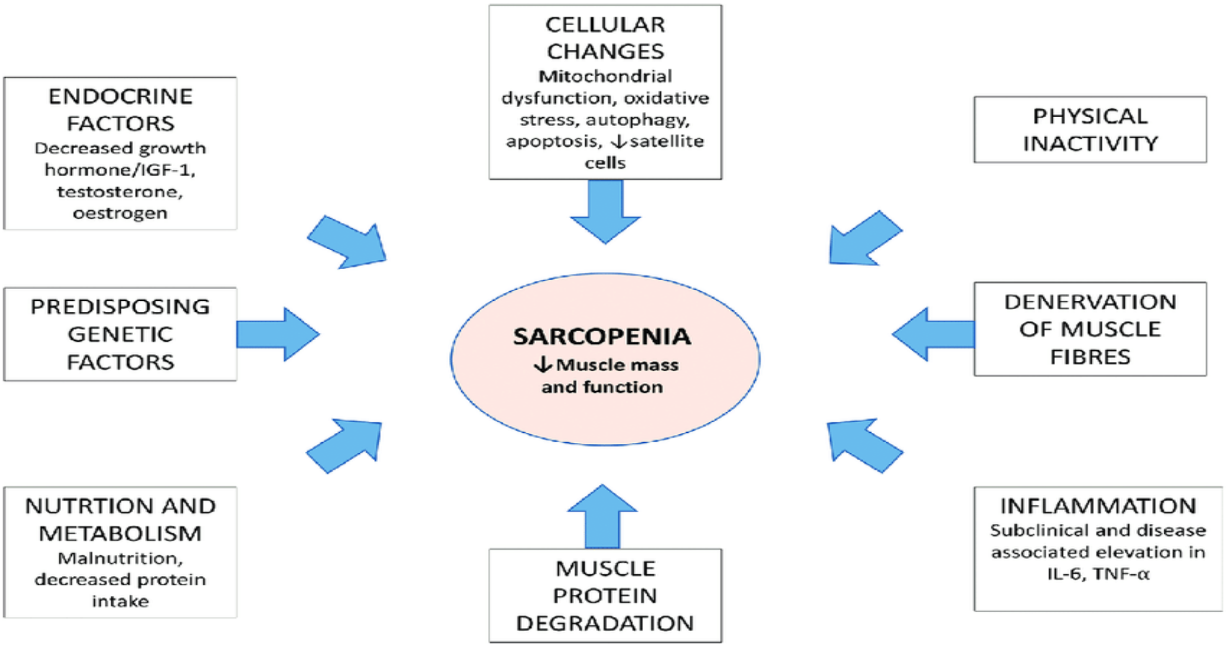

Fig. 81. Epidemiology of sarcopenia [Patel H., et al. 2017]

A study of 1250 Framingham Heart Study patients examined the relationships of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) assessed by CAT with circulating biomarkers of inflammation and oxidative stress (52% women; age 60±9 years). Biomarkers were studied in relation to increases in SAT and VAT indicators, after adjustment for age, sex, smoking, physical activity, menopause, hormone replacement therapy, alcohol and aspirin use; additional models include body mass index and waist circumference. SAT and VAT were positively correlated with C-reactive protein, Fibrinogen, Intercellular adhesion molecule-1, Interleukin-6, P-selectin, and Tumor necrosis factor receptor-2 (multivariate model R2 0.06 for 0.28 (SAT) and 0.07 for 0.29 (VAT).Dependence of VAT with Urinary isoprostanes and Monocyte chemoattractant protein-1 (SAT in norm, for variations of VAT comparison: isoprostanes, R2 0.07 vs. 0.10, P=0.002; monocyte chemoattractant protein-1, R2 0.07 vs. 0.08, P=0.04).When body mass index and waist circumference were added to the models, VAT remained significantly associated only with C-reactive protein (p=0.0003 for women; p=0.006 for men) [Pou K., et al. 2007] In the patients examined by us, we found high values of the laboratory parameters defining the inflammatory process, which gives grounds for comparability of the obtained results with the scientific database:

- in patients with Pancreatitis (p=0.042) with 0.73%.- SUE - OR =0.76%, in the confidence interval of 95%; CRP - OR =0.70%, at the 95% confidence interval; Lev - OR =0.89%, in the 95% confidence interval;
- in more than half of the patients with Ca of the lung, there is a risk of developing an infection due to the invasion of the colon carcinoma and the ongoing chemotherapy (for the 25th percentile - CRP is 13.97 mg/l, with 14 patients having very high values of the indicator (p=0.012);
- in the group of patients with Colorectal carcinoma, inflammatory changes were found preceding and accompanying the main disease, which gives an additional burden to the general condition;
- in the control group, a significant relationship was observed between the condition at hospitalization, the severity and duration of the disease, which determines the outcome of the disease and the hospital stay. Severe general condition is more common in patients with longer disease duration (12 months/or less);

This reduces the patient's quality of life and increases the days of incapacity. Current data support the association of SAT and VAT with inflammation and oxidative stress.

Karla M. Pou and her team define the relationship between obesity is a state of chronic inflammation characterized by elevated concentrations of circulating inflammatory markers. Based on 10 prospective studies, they demonstrate the association between C-reactive protein (CRP) and Interleukin (IL)-6 with an increased risk of diabetes mellitus and cardiovascular disease. It is clearly defined that inflammation is the critical link between obesity and obesity-related diseases such as insulin resistance, diabetes mellitus, hypertension and dyslipidemia [Pannacciulli N, et al. 2001; Mohamed-Ali V, et al. 1997; Festa A, et al. 2002; Ridker PM, et al. 2000; Mokdad AH, et al. 2003; Mokdad AH, et al. 2001; Harris MM, et al. 2000; Wilson PW, et al. 2002; Lemieux I, et al. 2000; Pascot A, et al. 2001].

Unlike subcutaneous adipose tissue (SAT), lipid deposition in VAT is associated with insulin resistance, dyslipidemia, chronic inflammation, hypertension, and physical dysfunction [Brinkley et al., 2012; Goodpaster et al., 2000; Siervo et al., 2016; Tchkonia et al., 2013], resulting in an increased risk (OR) of mortality within each body mass index (BMI) category [Cerhan et al., 2014; de Hollander et al., 2012; Santanasto et al., 2017]. Older individuals show systemic lipolysis and fat oxidation upon feeding, but less lipid storage in the SAT compared with younger individuals, according to a study using mCi [l-14C] to trace fatty acids [Koutsari C et al. 2009]. Through long-term measurements of adipose tissue, an inability of SAT to store excess energy is found, which initially leads to deposition of lipids in other ectopic depots (eg, skeletal muscle, liver, pancreas, heart) and cellular overwork. [Despres JP, & Lemieux I, 2006]. After a period of accumulation of adipose tissue, development of insulin resistance, massive weight loss follows due to the prolonged activation of inflammation predictors (macrophages, phagocytes, interleukins, T-helpers [Spalding KL, et al. 2008]. In the examined patients, it was established after 16 weeks of weight gain, adipocyte hypertrophy [Salans LB, et al. 1971].Хроничния положителен енергиен баланс, характерен за затлъстяването изостря възпалителните процеси в мастните депа [Zamboni M, et al. 2014]. Прекомерният калориен товар води до разширяване на мастната тъкан, чрез адипоцитна хипертрофия и хиперплазия [Kim SM, et al. 2014].

Low values of VAT were measured compared to those of SAT, a feature that partly explains the strict association between central obesity and disturbed metabolic profiles [Giordano A, et al. 2013]. Pro-inflammatory macrophages (Type 1) and T-cells infiltrating adipose tissue increase and establish the typical chronic (continuous) inflammation seen in the elderly (inflammaging), [Lumeng CN, et al. 2011]. In addition to inflammation, obesity-induced adipocyte hypertrophy is associated with abnormalities in tissue remodeling ie. overproduction of extracellular matrix components, reduced angiogenesis, fibrosis and hypoxia that profoundly compromise tissue microenvironment and function [Cancello R, et al. 2005]. Pro conducting a proper nutritional regime in obese patients, an improvement of the measured indicators of SAT, as well as a lower expression of oxidative stress markers and a reduced infiltration of proinflammatory macrophages compared to the control groups were found. In patients without dietary correction, direct disposal of excess free fatty acids into the portal circulation is observed, whereby lipid overload enriches the liver (often causing non-alcoholic fatty liver steatosis or NASH), which directly leads to lipotoxicity and muscle dysfunction. , due to an inflammatory effect on the skeletal muscles [Cizkova T, et al. 2020]. A long-term study conducted in men aged 70-79 years showed that fat loss in the thigh muscles had a strong protective effect against the inflammatory effects of VMP and the onset of sarcopenia, and a reduction in the OR for mortality in men with stable weight indicators and BMI [Santanasto AJ, et al. 2017].

All studies show that age-related changes in body composition, the appearance of chronic infections due to impaired caloric intake (weight loss or gain, the presence of accompanying diseases), lead to muscle fat infiltration and pathological lipid metabolism, leading to weakness and disability [Batsis JA, & Villareal DT. 2018]. CT-detected lipid infiltration into muscle fibers (intramyocellular) and/or stored in the adipocytes located between the fibers (extramyocellular) results in decreased muscle fiber contractility. This excess "energy" is strongly associated with insulin resistance leading to sarcopenia, disability, hospitalization and reduced quality of life. This causes continuous local inflammation, contributing to muscle loss. In addition, inflammatory cytokines reduce myocyte responsiveness to insulin-like growth factor 1 (IGF1), thereby impairing muscle anabolic pathways [Hamrick MW., 2017; Goodpaster BH, et al. 2000].

Fig. 82. Sarcopenia and infections as a factor in the reduction of muscle mass [Wicks S., et al. 2018]

Changes in SAT measurements are more important for diagnosis, while VAT measurements have no relation to activation of inflammatory processes in the body. Our study found that 90% of subjects had an accompanying disease, and 95% had evidence of infection (85% local and 10% with sepsis) ($p=0.002$).

We found a high risk of developing sarcopenia (1.07%) in patients with type 2 diabetes mellitus (in n=76 at 95% confidence interval), with 98% of them reporting the presence of an infection, with the risk increasing two-fold in the presence of insulin resistance (n=96), which increases the risk of liver damage and heart disease.

The inflammatory process has various effects on the body, not only in relation to the general condition, but also by affecting subcutaneous and visceral adipose tissue, bone density, which are predictors of sarcopenia.

CONCLUSIONS

1. A significant difference and dependence between the volume and density of subcutaneous and visceral adipose tissue and the diseases in the considered group of patients was established. An inverse relationship was reported between the volume and density of subcutaneous and visceral adipose tissue, with an increase in volume leading to a decrease in density, more pronounced for visceral adipose tissue.

2. A significant difference and moderate correlation between HUAC and staining was found in the studied groups of patients: the lowest values were found in patients with colorectal carcinoma (40.5) and the highest value was found in individuals from the control group (48.57). Female gender and advanced age are associated with a higher risk of developing sarcopenia. In patients with colorectal cancer, female gender is a risk factor for the development of sarcopenia ($OR=2.1$ (0.381-11.589); $p<0.05$), while in patients with lung cancer, male gender is a risk factor for the development of sarcopenia ($OR=2.5$ (0.370-16.888); $p<0.05$).

3. A moderate correlation was found between female gender and Psoas Index and an inverse moderate correlation between age and Psoas Index in males.

4. A statistical relationship was established between bone density and gender ($r=-0.454$; $p<0.001$), which shows that it decreases in women. In both sexes, a directly proportional moderate relationship between L3 body bone density and age was found.

5. In patients with sarcopenia, statistically significant differences were found in the volume of subcutaneous and visceral tissue in both sexes: higher values of the volume of subcutaneous adipose tissue in women (9824.08 cm3 vs. 8814.34 cm3) and lower in men (5245.36 cm3 to 6016.25 cm3): higher values of visceral adipose tissue volume in both women (4864.45 cm3 to 3642.92 cm3) and men (5497.85 cm3 to 5198.25 cm3).

6. A statistically significant relationship was found between VAT, L3 bone density, SAT and inflammatory markers and glucoselevels: increased VAT volume was associated with increased CRP values, decreased L3 bone density was associated with high values of ESR and blood glucose levels correlate inversely with subcutaneous fat volume and directly with BMI density.

CONCLUSION

There are some limitations in our study. In terms of underlying etiology and etiologic risk factors, the defined cohorts were reviewed retrospectively and comparable outcomes were reported in terms of a range of phenotype and demographics and subsequently clinical data measured in clinical laboratory and imaging studies.

Cohorts were comparable with respect to outcome of hospital stay, bed days, and risk of developing sarcopenia depending on the nature and invasiveness of the underlying disease. Sarcopenia for all groups is characterized by an age-related decrease, but also as a pathological sign in socially significant diseases CVD, COPD, cancer and others, and is described as a syndrome of weakness, describes the general decline in physiological reserve associated with loss of muscle mass and in disorders of basic functions that make the patient vulnerable to diseases.

Many of the factors relevant to disease development were the same for the cohorts. Comprehensive diagnosis requires a detailed anamnesis, a study of the nutritional and movement regime, conducting imaging studies, regardless of the reason for the individual's visit or hospitalization. Among the interventions at the different levels of medical care is timely influencing the lifestyle, to more effectively improve the quality of the myocellular cells and the individual's response to the changed internal environment, thus preserving the physiology of the muscle mass and alleviating the weakness. Such lifestyle intervention can be considered an effective strategy to reduce the metabolic changes and physical complications associated with aging and obesity, with the ultimate goal of maintaining the functional independence and quality of life of the elderly to impact sarcopenic obesity. , one of the major health care challenges of this century, affecting an increasing proportion of the elderly. Bone health: inflammatory conditions such as rheumatoid arthritis can directly affect joint and bone health. Systemic inflammation can disrupt the balance between bone formation and resorption. The contributions of our research, comparable to international literary sources, reveal the practical and scientific nature of the results. The established relationships between weight, BMI, visceral and subcutaneous adipose tissue measurements, together with collected and analyzed data on current or previous diseases, define a worsened prognosis for healthy SLE due to the high OR risk for sarcopenia. Measured high values of VAT are associated with various health problems, including cardiovascular disease and diabetes. SAT and VAT itself can produce inflammatory cytokines, creating a cycle of inflammation, and inflammatory markers can contribute to triggering insulin resistance, promoting fat storage, especially visceral fat. Chronic inflammation can lead to increased bone resorption and decreased density, which contributes to osteoporosis. Inflammatory cytokines TNF-alpha and IL-6 negatively affect bone density by affecting bone remodeling processes (breakdown of muscle protein, which contributes to muscle loss).

It is important to note that these processes are interconnected (the relationship between inflammation and these physiological parameters is complex). Chronic inflammation is often a component of a variety of diseases, and managing inflammation through lifestyle interventions, medications, or other therapies can positively impact these health outcomes. However, specific mechanisms may vary depending on underlying conditions and individual factors. Therefore, it is important to act in the early stages of diagnosis, through physical activity, a balanced diet, which have the potential to mitigate the impact of inflammation on adipose tissue, bones and muscles.

CONTRIBUTIONS

Contributions of a theoretical nature

1. 1. For the first time in Bulgaria, the application of low-dose CT of the abdomen and other imaging methods (US, DEXA and MPI) in the assessment of abdominal fat, bone density and sarcopenia has been reflected in detail.

Contributions of a practical and applied nature

1. A difference in the ratios and correlations between subcutaneous and visceral adipose tissue with bone density and sarcopenia was found in men and women.
2. A bone density assessment phantom has been created that can also be applied in outpatient settings.
3. It was established that some indicators of the inflammatory process correlate with the volume of visceral fat tissue and bone density indicators in the patients with the investigated oncological diseases.
4. It has been shown that CT can be a reliable, non-invasive method for assessing abdominal adipose tissue, bone density and sarcopenia in patients with some types of oncology and chronic pancreatitis.
5. Our methodology can be widely used in the future in gastroenterology, in endocrinology to monitor the therapeutic response of applied obesity treatment, in surgery, in oncology and in clinical trials of new oncological drugs to monitor the therapeutic response to chemotherapy.

Contributions of an original nature

1. For the first time in Bulgaria, a CT assessment of abdominal adipose tissue, bone density and sarcopenia in patients with oncological diseases and chronic pancreatitis was carried out.
2. For the first time in Bulgaria, the relationship between the indicators from the CT assessment of abdominal fat tissue, bone density and sarcopenia has been described.

PARTICIPATION IN PROJECTS RELATED TO THE DISSERTATION

1. ***"Clinical significance of abdominal visceral adipose tissue in patients with breathing disorders during sleep"*** *with supervisor Prof. Dr. Diana Petkova Gospodinova-Valkova, MD,PhD*

DISSERTATION RELATED PUBLICATIONS

1. Georgi Valchev, Dimitrina Markova, Daniela Kaloyanova, Summer El Shemeri, Sofia Chausheva, Marianna Yordanova. Visualization and post-processing of medical images – MPR, MIP, VRT, segmentation. Nature and application. Varna Medical Forum, Volume 10, 2021, Appendix 1; 64-72.
2. Dimitrina Markova, Georgi Valchev, Tanya Dobreva-Kuncheva. Application of imaging methods in the study of the influence of sleep apnea on abdominal adipose tissue - review of the literature, Health & Science, 2023, year XII, issue 3-4 (045-046), pp. 259-261.
3. Dimitrina Markova, Georgi Valchev. Imaging methods for the diagnosis of sarcopenia. Varna Medical Forum, Item 12, 2023, Issue 1, Pages 12-20

PARTICIPATION IN SCIENTIFIC FORUMS

1. IX Scientific Session of MK - Varna, 26.03.2021, city of Varna
2. Jubilee Scientific Conference "Traditions and Future in Medical Education" with international participation, 21.03.2023, Sofia